The Journal of Pediatrics

VOL. 39 . SEPTEMBER, 1951 No. 3

THE EFFECT OF CORTISONE ON NUTRITION

LIEUTENANT COLONEL LEO J. GEPPERT, CAPTAIN BERNARD F. O'HARA, AND CAPTAIN A. C. PEAT, MEDICAL CORPS, UNITED STATES ARMY

WITH THE TECHNICAL ASSISTANCE OF JANE NEFF, B.A., AND ADDELIA PETERSON, M.T.

MOST of the published reports on ACTH and cortisone are concerned with the antirheumatic and antipyretic effects of these substances. The biochemical metabolic effects are usually considered undesirable. The published report of Hench, Kendall, Slocumb, and Polley[1] has emphasized that what may be undesirable in one patient may be desirable in another. These authors report that one of the earliest effects of cortisone is stimulation of appetite with gains in weight. Of twenty-one patients given cortisone twenty had increased appetites, and for eleven patients the increase in appetite was insatiable. The intake of one patient on a free diet was checked and found to be 6,000 calories a day. According to these authors, patients receiving cortisone experienced two types of gain; a progressive nutritional gain not quickly diminished when cortisone was discontinued, and rapid, fluctuating, unstable weight gain due to the retention of fluid which disappeared quickly within a few days after cortisone was discontinued. They concluded that it was not easy to distinguish between the two types of weight gain or to estimate how much of the increased weight gain was due to improved nutrition. The following investigations were undertaken to define more exactly the partition of the weight gain between nitrogen retention and fluid retention when cortisone is administered.

From the Pediatric Service, Brooke Army Hospital, and the Fourth Army Area Medical Laboratory, Brooke Army Medical Center, Fort Sam Houston, Texas.

Part of the cortisone for this study was provided through the courtesy of Augustus Gibson, M.D., Associate Medical Director, Merck & Co., Inc.

PROCEDURE AND METHODS

Intake.—The following balance studies were accomplished by offering patients scheduled for cortisone therapy the following qualitatively standard diet:

Breakfast	*Grams*
Orange juice	100
Dry cereal	15
Fat-free eggs	100
Bread	30
Butter	10
Sugar	5
Whole milk	240
Lunch	
Chopped beef	45
Fat-free potatoes	67
Lettuce	50
Canned peaches	100
Bread	15
Butter	10
Whole milk	240
Dinner	
Chopped beef	45

Potatoes	67
Tomatoes	50
Canned applesauce	100
Bread	15
Butter	10
Whole milk	240
8 P.M. Nourishment	
Ice cream	70
Unsalted crackers	16

All rejects were accurately weighed as were the additional amounts consumed by the patients on an unlimited intake. The average values for sodium, potassium, and nitrogen contents of foodstuffs were obtained from standard tables. According to Reifenstein, Albright, and Wells[2] this introduces a possibility of at least a 10 per cent error but the order of magnitude of the changes is so great that this error does not invalidate the data.

Chemical Analysis of Excretions.—Urine and stool collected over seventy-two- or ninety-six-hour periods were analyzed quantitatively for nitrogen, potassium, sodium, chloride, creatinine, uric acid, 17-ketosteroids, volume, and specific gravity. After short base line studies, collections were made during the period of cortisone administration and were continued until the effect of the steroid on appetite was no longer evident. The chemical methods used by the Fourth Army Area Medical Laboratory were as follows: Total nitrogen, Folin; chloride, Schales and Schales; potassium, Breh and Gaebler; sodium, the uranyl magnesium acetate procedure of the Army Medical School; creatinine, Folin; uric acid, Benedict and Franke.

This study was conducted on two 4-year-old white males who had rheumatoid arthritis, and one 11-year-old white male who had biliary cirrhosis and pancreatic fibrosis.

CASE REPORTS

CASE 1 *(Chronic Rheumatoid Arthritis).*—This 4-year-old white male was first referred to Brooke Army Hospital on April 29, 1949, because of a history of unexplained fever of eight months' duration. The fever had been intermittent with bouts lasting approximately one week and separated by intervals varying from a week to ten days. On many occasions during these episodes of fever a nondescript macular erythematous rash was noted over various parts of the body. Family history and past history were noncontributory except for a history of a systolic murmur which has been present since birth.

At the time of the first admission the patient was 3½ years of age, weighed 29 pounds, and was 38 inches tall. He appeared both acutely and chronically ill. Although the patient complained of joint pains there was no objective evidence of joint involvement. There was a generalized, nontender lymphadenopathy present. A grade 2 systolic murmur, not transmitted, was heard best in the second left interspace. Repeated white blood cell counts varied from 10,000 to 13,000 with 60 per cent of the cells being polymorphonuclear. The red blood cell count varied from 3.5 to 4.5 million per cubic millimeter. The average hemoglobin determination was 11.5 Gm. with a hematocrit of 40 vol. per cent. The sedimentation rate was consistently elevated with the determinations varying from 38 to 52. Repeated examinations showed the urine to be normal. Repeated urine cultures were negative. Twelve blood cultures drawn at three-day intervals showed no growth in any type of media. No pathogenic bacteria, ova, or parasites could be found in the stools. The skin test for tuberculosis was negative. Spinal fluid was normal. Blood urea nitrogen was 15 mg. per cent and intravenous pyelograms were normal. Urobilinogen was present in normal amounts in the stool. Repeated agglutinations were negative for ty-

phoid, paratyphoid, brucella, tularemia, OX_{19}, OX_2, and OXK. The histoplasmin skin test was positive at twenty-four and forty-eight hours but the complement fixation test was negative. Skeletal surveys and x-rays of the skull, chest, and spine were normal. The bone marrow was somewhat hypoplastic. Bone marrow cultures were negative. Serial electrocardiographic tracings were within normal limits. Beta hemolytic streptococci was the predominating organism found in throat cultures.

The child maintained a septic febrile course with daily elevations of temperature to 104° F. No improvement resulted from penicillin or streptomycin therapy. The diagnosis remained in doubt until June 25, 1949, when joint changes typical of rheumatoid arthritis were noted in the patient's wrists, interphalangeal joints, ankles, and spine. Supportive treatment, including repeated blood transfusions, did not improve the patient's condition. Aureomycin in doses of 50 mg. per kilogram of body weight was started on July 7, 1949. On the first day of this treatment the patient's temperature became normal and remained so as long as the drug was continued. There was, however, no concurrent improvement in the joint involvement. A course of Teropterin was given for ten days without any changes resulting. The patient was discharged on Sept. 12, 1949.

On Aug. 1, 1950, the patient was readmitted for cortisone therapy. At the time of this admission he was found to be 4 years, 9 months of age, weighed 30 pounds, and was 40 inches tall. His temperature was 102° F. The grade 2 systolic murmur was noted to be unchanged during the eighteen months this patient had been followed. Sedimentation rate was 36 mm. per hour. White blood cell count was 12,000 with 60 per cent polymorphonuclears and 37 per cent lymphocytes. The red blood cell count was 3.4 million with 11 Gm. of hemoglobin. Eosinophiles were reduced from 40 to 0 per cubic millimeter four hours after a test dose of Adrenalin. 17-Ketosteroid secretion averaged 1.1 mg. per day over a control period of seven days. Cortisone* was started on Aug. 12, 1950. Although the weather was stormy at this time and the patient had rather severe swelling, pain and tenderness in the involved joints, symptomatic relief was noted within twelve hours. The dose of cortisone used was 200 mg. per twenty-four hours for three days, after which it was cut to 100 mg. per twenty-four hours for twelve days. The dose was then cut to 50 mg. and kept at this level for an additional eleven days. The total dose was 2.3 Gm. over a period of twenty-seven days. The results of therapy are summarized in Fig. 1. During this period there was a definite increase in range of motion in fingers, wrists, elbows, knees, ankles, and back. The fixation of the left hip was only moderately relieved so that the patient continued to limp. There was a definite decrease in the degree of swelling of the affected joints. The patient was afebrile after twenty-four hours of therapy and remained so for approximately ten days following cessation of therapy. The sedimentation rate returned to normal while the patient was receiving full doses of cortisone, but rose to 40 mm. per hour when the dose was cut to 50 mg. per day. A blood pressure rise to a maximum of 150/90 was noted. 17-Ketosteroid secretion increased to 3.5 mg. per twenty-four hours. Fasting blood sugar was within normal limits during the course of therapy but there was a decreased glucose tolerance ten days after cortisone was discontinued. There were no significant changes in serum sodium, chloride, or bicarbonate. Serum potassium reached a low of 2.9 meq. two days after therapy was discontinued, but serial electrocardiograms showed no evidence of hypokalemia. No abnormality of cephalin flocculation, serum bilirubin, or thymol turbidity was noted. There

*Cortone Acetate, Merck & Co., Inc.

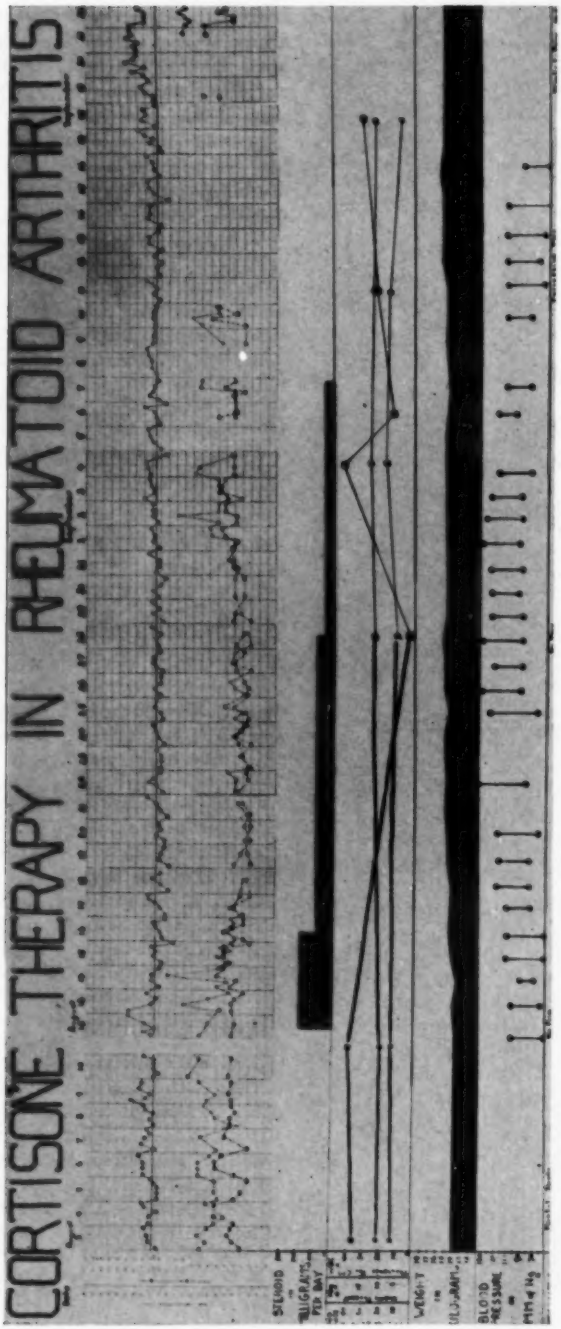


Fig. 1 (Case 1).—First course of therapy.

TABLE I. METABOLIC CHANGES FROM CORTISONE THERAPY. INTAKE LIMITED TO 1,900 CALORIES. AVERAGE DAILY BALANCES OF ELECTROLYTES AND NITROGEN

Base Line Studies

STUDY DAYS	CALORIES PER 24 HR.	NITROGEN (GM.) IN	NITROGEN (GM.) OUT	NITROGEN (GM.) BAL.	SODIUM (mM) IN	SODIUM (mM) OUT	SODIUM (mM) BAL.	POTASSIUM (mM) IN	POTASSIUM (mM) OUT	POTASSIUM (mM) BAL.	CORTISONE MG./DAY
1-6	1,500	8.9	6.7	2.2	65.2	62.4	2.8	35.9	30.3	5.6	None
Total				12.12			16.8			33.6	

Nitrogen gain for study period 12.12 grams × 29.2 = 353.9 grams protoplasm
Sodium gain 16.8 mM ÷ 151 × 1,000 = 111 grams − 61 (12.12 × 5) = 50.0 grams extracellular fluid
Potassium gain 33.6 mM ÷ 143 × 1,000 = 235 grams − 230.3 (12.12 × 19) = 4.7 grams intracellular fluid

Theoretical weight gain	408.6 grams
Actual weight gain	471.0 grams
Caloric discrepancy	62.4 grams error or fat

Recrudescence of Acute Rheumatoid Arthritis—Cortisone Therapy Started

STUDY DAYS	CALORIES PER 24 HR.	NITROGEN (GM.) IN	NITROGEN (GM.) OUT	NITROGEN (GM.) BAL.	SODIUM (mM) IN	SODIUM (mM) OUT	SODIUM (mM) BAL.	POTASSIUM (mM) IN	POTASSIUM (mM) OUT	POTASSIUM (mM) BAL.	CORTISONE MG./DAY
1-3	850	5.5	5.25	0.25	28	26	2	33	33	0	200
4-6	1,524	9.0	8.99	0.01	54	31	23	41	58	−17	100
7-9	1,900	13.5	12.85	0.65	70	45	25	66	64	2	100
10-12	1,900	13.5	13.4	0.10	70	54	16	66	93	−27	100
13-15	1,900	13.5	12.9	0.61	70	56	14	66	65	1	100
16-18	1,900	13.5	12.86	0.64	70	58	12	66	37	29	100
19-21	1,900	13.5	12.96	0.54	70	101	−31	66	50	16	50
22-24	1,900	13.5	11.7	1.80	70	103	−33	66	44	22	50
25-27	1,900	13.5	9.4	4.10	70	75	− 5	66	37	29	50
28-30	1,900	13.5	7.2	6.30	70	69	1	66	45	21	0
31-33	1,900	13.5	5.6	7.90	70	68	2	66	60	6	0
Total				68.70			78			246	2,550

Nitrogen gain for study period 68.7 grams × 29.2 = 2,006.04 grams protoplasm
Sodium gain 78 mM ÷ 151 × 1,000 = 516 grams − 343.5 (68.7 × 5) = 172 grams extracellular fluid
Potassium gain 246 mM ÷ 143 × 1,000 = 1,720 grams − 1,305 (68.7 × 19) = 415 grams intracellular fluid

Theoretical weight gain	2,593 grams
Actual weight gain	2,495 grams
Caloric discrepancy	100 grams error or fat

Patient G. J. Aged 4 9/12 years. Height 102 cm.

Weight at start of study	13,608 grams
Weight at completion of study	16,103 grams
Basal caloric requirements	800
Total caloric intake above requirements	8,100

was some increase of serum protein chiefly because of a rising albumin fraction.

Balance Studies.—This patient developed a marked increase in appetite but caloric intake was not allowed to exceed 1,900 calories per day so that his total weight gain was only 2,495 grams. Table I summarizes the balance studies conducted.

CASE 2. *Acute Rheumatoid Arthritis.*—This 4-year-old white male had been followed in the Outpatient Clinic at Brooke Army Hospital since birth and was known to be well until five days before admission to the hospital. On March 24, 1950, he developed acute tonsillitis associated with a temperature of 105° F. When he failed to respond to adequate doses of antibiotics after five days he was admitted to the hospital for further investigation and treatment. His mother and father are living and well and the patient has no siblings. There was no history of familial or hereditary disease. Past history was uncomplicated and noncontributory.

Physical examination on admission to the hospital was essentially negative. Height was 41 inches, weight was 31 pounds. Temperature was 102.4° F. There was no apparent explanation for his fever.

White blood cell count varied from 15,000 to 31,000 per cubic millimeter, 80 per cent of these cells being polymorphonuclear, and 20 per cent lymphocytes. The red blood cell count averaged 3.9 million per cubic millimeter with a hemoglobin of 11.5 Gm. Sedimentation rate was consistently over 25 mm. per hour and went as high as 50. The urine was normal.

Since this patient seemed to have an acute septic type of illness a thorough search was made for an etiological agent. Repeated cultures of blood and urine were negative on all types of laboratory media. No bacteria, virus, or rickettsiae were recovered from animals or eggs inoculated with both blood and bone marrow. Both thick and thin malarial smears were examined before and after Adrenalin but no malarial parasites were ever discovered. No pathogenic agents could be seen in bone marrow sections. Stool cultures were negative for ova, parasites, and pathogenic bacteria. Skin tests for tuberculosis and histoplasmosis were negative. Spinal fluid was normal. Agglutinations for typhoid, paratyphoid, brucella, tularemia, OX_{19} and OX_2 and heterophile antibody were repeatedly negative. Beta hemolytic streptococci were the predominating organisms in throat culture.

The patient continued to run a septic type of fever with daily spikes up to 106° F. despite therapy with penicillin, streptomycin, sulfadiazine, aureomycin, and Chloromycetin, singly and combined. Sodium salicylate was given in doses adequate to produce blood levels up to 30 mg. per cent without improvement. Electrocardiographic tracings at three-day intervals showed a persistent heart rate between 220 and 240 until the patient was digitalized during the third week of his illness. Ten days after admission the patient developed bilateral pneumonitis and a pericardial friction rub. A grade 2 systolic murmur was heard at the apex for several days. A nondescript erythematous rash was noted at various times during this period. Although this patient was suspected of having an acute variety of the rheumatic state the diagnosis could not be definitely substantiated until April 18, 1950, one month after the onset of his illness. At that time the patient furnished the diagnosis by developing changes in the small joints of the fingers, hands, and wrists which were characteristic of rheumatoid arthritis. In the next few days the knees and back also became involved. No arthritic changes could be detected on the x-rays of these joints.

On May 1, 1950, the patient was transfused with fresh blood from a convalescent scarlet fever patient with no improvement. Neither was improvement noted after the patient was transfused with 200 c.c. of blood from

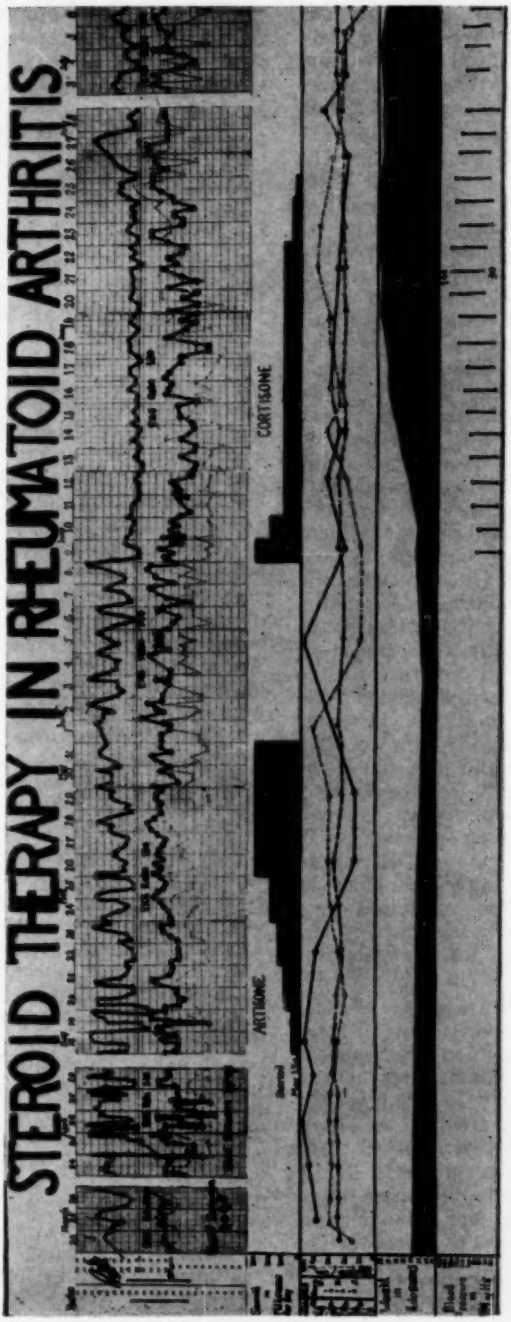


Fig. 2 (Case 2).—First course of therapy.

post-partum patients daily for four days. The patient remained acutely ill and wasted rapidly despite supportive treatment. Further progress of this patient is summarized in Fig. 2.

Treatment With Artisone.—Artisone*[3] was started on May 18. The daily dose of 50 mg. was divided into equal parts and administered at twelve-hour intervals. This was increased by increments of 50 mg. every two days so that the patient was receiving 300 mg. per day by the ninth day. Dosage was maintained at this level for six more days. The total amount given was 3,100 mg. No adverse side effects were noted. No clinical improvement was detected. However, while the patient was receiving the maximum dose of 300 mg. a day the sedimentation rate dropped from 50 to 15 mm. per hour. Before this steroid was administered the patient had no circulating eosinophiles and there was no change in uric acid/creatinine ratio following Adrenalin. After Artisone was discontinued the patient had 200 eosinophiles per cubic millimeter but still no response to Adrenalin. The sedimentation rate rapidly increased to 50 mm. per hour after Artisone was discontinued. An increase in ketosteroid excretion from 1.76 mg. per twenty-four hours to 2 mg. per twenty-four hours followed therapy. There was no change in glucose tolerance test and the values for serum sodium, potassium, chloride, bicarbonate, protein, and blood urea nitrogen remained normal. The patient continued to lose weight, was acutely ill and very miserable.

Treatment With Cortisone.—After base line studies were completed the patient was started on cortisone on June 9, 1950. The dosage was 300 mg. for the first twenty-four hours, 200 mg. for the second twenty-four hours, and 100 mg. daily thereafter. The dramatic response is evident in Fig. 2. Within twelve hours the temperature returned to normal and remained normal during the course of therapy. The cardiac rate also approached normal ranges for the first time since the onset of his illness. He appeared much brighter, less miserable, and no longer complained of pain. His appetite improved remarkably so that it was no longer necessary to feed him by tube. He ceased what had been a constant querulous whining. The generalized lymphadenopathy which had been very marked was not notable by the third day. The improvement in his joints was so remarkable that after forty-eight hours of therapy he was able to walk across the ward without assistance. He was also able to feed himself for the first time in three months. His wrists remained somewhat swollen but normal mobility was resumed. Pain was absent. Sedimentation rate dropped from 50 to around 20 mm. per hour. There was a slight rise in hemoglobin and red cell count. The white blood cell count actually rose from 15,000 to 39,000 without noticeable change in differential during this course of treatment. An increase in blood pressure to a maximum of 140/90 was noted. The hypertension rapidly disappeared after cortisone was discontinued. After ten days of therapy when the patient had developed a partial Cushing's syndrome, marked enlargement of the liver was discovered. Prothrombin time increased to 27 with a control of 18. There was an 8 per cent retention of bromsulfalein after one hour. Cephalin flocculation test was slightly positive (at forty-eight hours). Thymol turbidity increased from 1.75 to 7 units. There was no change in serum cholesterol. The abdomen was very distended but no fluid was found on paracentesis. Flat films of the abdomen showed marked gaseous distention. Glucose tolerance remained normal. There were no significant changes in serum sodium, potassium, chloride, or bicarbonate. Electrocardiographic tracings at three-day intervals showed no evidence of hypo- or hyperkalemia. While the patient was receiving cortisone there

*Artisone, Wyeth Incorporated.

TABLE II. METABOLIC CHANGES FROM CORTISONE THERAPY. FREE DIET, UNLIMITED INTAKE. AVERAGE DAILY BALANCES OF ELECTROLYTES AND NITROGEN

Base Line Studies

STUDY DAYS	CALORIES PER 24 HR.	NITROGEN (GM.)			SODIUM (mM)			POTASSIUM (mM)			CORTISONE MG./DAY
		IN	OUT	BAL.	IN	OUT	BAL.	IN	OUT	BAL.	
1-3	1,567	7.5	7.4	0.1	42	39	3	38	38	0	None
Total				0.3			9				

No appreciable weight change, theoretical or actual.

Acute Rheumatoid Arthritis, Temperature 106° F. Cortisone Therapy Started.

STUDY DAYS	CALORIES PER 24 HR.	NITROGEN (GM.)			SODIUM (mM)			POTASSIUM (mM)			CORTISONE MG./DAY
		IN	OUT	BAL.	IN	OUT	BAL.	IN	OUT	BAL.	
1-3	1,677	7.4	6.56	0.84	53	30	23	52	41	11	200
4-7	2,250	12.5	8.15	4.35	75	24	51	78	88	−10	100
8-11	3,000	13.1	8.54	4.56	112	84	28	99	67	32	100
12-15	3,752	19.38	13.0	6.38	120	87	33	107	92	15	100
16-18	3,131	15.5	12.6	2.9	107	141	−34	92	88	4	50
19-21	2,756	13.2	12.0	1.2	86	139	−53	81	60	21	None
22-24	2,663	12.3	11.4	0.9	75	88	−13	78	58	20	None
25-27	2,414	10.2	9.0	1.2	70	79	− 9	74	67	7	None
Total				82.28			190			337	1,950

Nitrogen gain for study period 82.28 grams × 29.2 = 2,402 grams protoplasm
Sodium gain 190 mM ÷ 151 × 1,000 = 1,258 grams − 411 (82.28 × 5) = 847 grams extracellular fluid
Potassium gain 337 mM ÷ 143 × 1,000 = 2,356 grams − 1,563 (82.28 × 19) = 793 grams intracellular fluid

Theoretical weight gain	4,042 grams
Actual weight gain	4,423 grams
Error or fat	381 grams

Patient D. B. Aged 4 years. Height 104.5 cm.

Weight at start of study	13,268 grams
Weight at completion of study	17,690 grams
Basal caloric requirements	800
Total caloric intake above requirements	30,791

were no circulating eosinophiles but one week after therapy was discontinued the patient had 325 eosinophiles per cubic millimeter before Adrenalin and 200 per cubic millimeter following Adrenalin. The uric acid/creatinine ratio changed from 1 before Adrenalin to 2.77 in the urine specimen collected for four hours after the injection of Adrenalin.

Cortisone was discontinued on June 25 after seventeen days of therapy, and a total dose of 1.8 Gm. The patient immediately became febrile and his joint symptoms and signs returned.

Balance Studies.—Chiefly because of a marked spontaneous increase in intake from 1,200 to 4,000 calories per twenty-four hours the patient gained a pound a day. The total weight gain was 4,423 grams. Serum albumin rose from 3.6 to 4.4 grams per cent and serum globulin from 2.78 to 4.89 grams per cent. Table II provides a summary of balance studies.

Second Course of Therapy.—Although the patient had a definite recrudescence of this disease as soon as cortisone was discontinued, the intensity of the process was markedly decreased (Fig. 3). His daily temperature elevation averaged 102° F. compared to 106° F. before therapy. His appetite decreased and there was a progressive loss of weight. The sedimentation rate gradually rose to 50 mm. per hour. Joint signs and symptoms were not marked until ten days after discontinuation of therapy. Blood pressure returned to normal levels within seven days after discontinuation of treatment. Eosinophile count fell from 128 to 22 per cubic millimeter four hours after Adrenalin. 17-Ketosteroid excretion during this interval was 1.5 mg. per twenty-four hours.

After the patient's weight had dropped from 42 to 33 pounds in a period of thirty-six days, cortisone therapy was resumed on July 31, 1950. Two hundred milligrams were given during the first twenty-four hours and 100 mg. per day for ten days thereafter. The dose was then diminished to 50 mg. per day for an additional seven days, and finally 25 mg. for two more days. Total dose of cortisone was 1.6 Gm. over a period of twenty days. The patient again became afebrile and remained so throughout the course of cortisone. The pain and tenderness in the patient's wrists and knees again disappeared within twenty-four hours and there was a steady increase in range of motion. Sedimentation rate again rose with treatment and remained in the neighborhood of 40 mm. per hour until treatment was discontinued. The white blood cell count returned to normal and remained so. Blood pressure again rose from 90/60 to a peak of 120/70. The enlargement of the liver was less remarkable during the second course of therapy but the patient again had 10 per cent retention of bromsulfalein after fifteen days of treatment. Thymol turbidity test rose from 3.7 to 7 units on the fifteenth day. There were no significant changes in cephalin flocculation or serum cholesterol. Serum albumin rose from 4.23 to 4.88 grams per cent. Serum globulin dropped from 4.89 to 1.78 grams per cent during treatment but rose to 2.3 grams per cent after treatment was discontinued. As the dose of cortisone was decreased, the excretion of 17-ketosteroids increased progressively from 1.5 to 4.5 mg. per twenty-four hours. Fasting blood sugars were within normal limits and the glucose tolerance test was normal after the completion of therapy. The patient's serum sodium was elevated as high as 147 meq. A serum potassium as low as 2.7 was recorded on the fifteenth day of therapy but serial electrocardiographic tracings showed no evidence of hypokalemia. The second course of cortisone was terminated on Aug. 19, 1950, without a recurrence of fever. He had no return of joint pain until September 5 when he developed some pain in his left elbow on extreme flexion. His appetite continued good and his weight gradually increased to 40 pounds. Blood pressure rapidly returned to normal

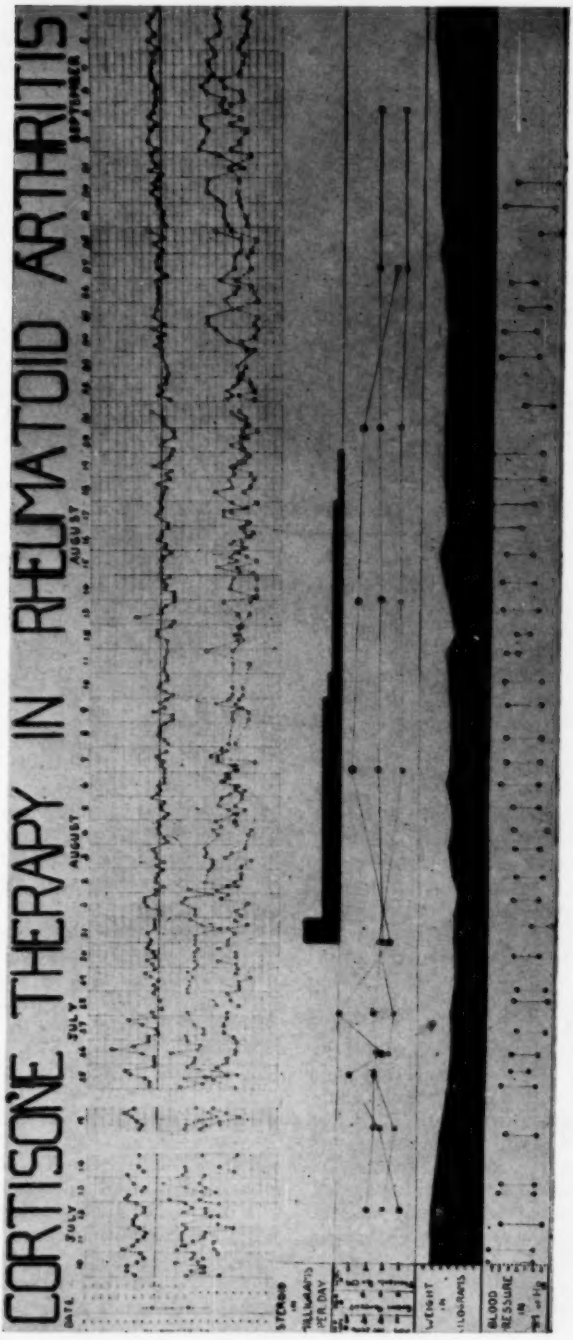


Fig. 3 (Case 2).—Second course of therapy.

TABLE III. METABOLIC CHANGES FROM CORTISONE THERAPY. INTAKE LIMITED TO 1,900 CALORIES.
AVERAGE DAILY BALANCES OF ELECTROLYTES AND NITROGEN

Base Line Studies

STUDY DAYS	CALORIES PER 24 HR.	NITROGEN (GM.) IN	NITROGEN (GM.) OUT	NITROGEN (GM.) BAL.	SODIUM (mM) IN	SODIUM (mM) OUT	SODIUM (mM) BAL.	POTASSIUM (mM) IN	POTASSIUM (mM) OUT	POTASSIUM (mM) BAL.	CORTISONE MG./DAY
1-3	850	5.07	5.3	−0.23	28	33	− 5	26	23	3	None
Total				0.69			−15			9	

Nitrogen loss for study period 0.69 grams × 29.2 = 20 grams protoplasm loss
Sodium loss 15 mM ÷ 151 × 1,000 = 100 grams − 10 (2 × 5) = 90 grams extracellular fluid loss
Potassium gain 9 mM ÷ 143 × 1,000 = 63 grams + 38 (2 × 19) = 101 grams intracellular fluid

Theoretical weight loss	9 grams
Actual weight loss	0
Caloric discrepancy	9 grams

Acute Rheumatoid Arthritis. Second Course of Cortisone Therapy After a 30-Day Rest Period

STUDY DAYS	CALORIES PER 24 HR.	NITROGEN (GM.) IN	NITROGEN (GM.) OUT	NITROGEN (GM.) BAL.	SODIUM (mM) IN	SODIUM (mM) OUT	SODIUM (mM) BAL.	POTASSIUM (mM) IN	POTASSIUM (mM) OUT	POTASSIUM (mM) BAL.	CORTISONE MG./DAY
1-4	1,050	6.0	5.43	0.57	42	39	3	33	78	−45	125
5-8	1,270	7.3	6.3	1.0	60	59	1	46	56	−10	100
9-11	1,780	10.67	9.16	1.51	68	51	17	59	55	4	100
12-14	1,912	13.5	9.8	3.7	70	62	8	66	39	27	50
15-17	1,912	13.5	12.6	0.9	70	51	19	66	43	23	50
18-20	1,912	13.5	13.13	0.37	70	75	−5	66	62	4	0
21-23	1,912	13.5	12.7	0.8	70	73	−3	66	44	22	0
24-26	1,912	13.5	10.2	3.3	70	72	−2	66	44	22	0
27-29	1,912	13.5	10.11	3.39	70	68	2	66	40	26	0
30-32	1,912	13.5	5.9	7.6	70	70	0	66	44	22	0
Total				70.99			124			230	1,500

Nitrogen gain for study period 70.99 grams × 29.2 = 2,072.9 grams protoplasm
Sodium gain 124 mM ÷ 151 × 1,000 = 821 grams − 355 (71 × 5) = 456 grams extracellular fluid
Potassium gain 230 mM ÷ 143 × 1,000 = 1,608 grams − 1,349 (71 × 19) = 259 grams intracellular fluid

Theoretical weight gain	2,787.9 grams
Actual weight gain	2,835 grams
Error or fat	47.1 grams

Patient D. B. Aged 4 years. Height 104.5 cm.

Weight at start of study	15,876 grams
Weight at completion of study	18,711 grams
Basal caloric requirements	800
Total caloric intake above requirements	7,092

values. The patient was discharged from the hospital on Sept. 7, 1950, in complete remission. His weight gradually stabilized at 36 pounds, which is normal for this patient.

Balance Studies.—Caloric intake was restricted to 1,900 calories per twenty-four hours to prevent excessive weight gain. Total gain was 2,835 grams. Balance studies are summarized in Table III.

CASE 3. *Biliary Cirrhosis and Pancreatic Fibrosis.*—This 10 year, 11 month old white male was admitted to Brooke Army Hospital on Aug. 11, 1950, because of gastrointestinal and respiratory symptoms. Although he had never had frank diarrhea his stools had been bulky, copious and foul smelling since birth. He had six to ten such bowel movements a day. For the past several years the patient had also had a chronic persistent productive cough not associated with upper respiratory infections, fever, or malaise. For the past few years at infrequent intervals the patient vomited his breakfast. Past history was noncontributory. Mother and father are living and well and there are no siblings.

Physical examination at the time of admission showed the patient to be physically retarded. His height was 51 inches and his weight was 50 pounds. His lips were cyanotic and his fingers and toes showed clubbing. Examination of the abdomen revealed a hard, somewhat irregular mass with a very definite edge in the epigastrium, extending approximately three inches below the xiphoid process almost to the umbilicus. This was thought to be the liver. The liver edge in the right mid-clavicular line was palpable, but only about one-half inch below the costal margin. The spleen was also palpable four finger breadths below the costal margin. Spider hemangiomas were noted about the neck and shoulders. Examination of the chest was negative.

The red blood cell count was 4,500,000 per cubic millimeter with a hemoglobin of 14 Gm. There were 6,600 white blood cells per cubic millimeter. Platelet count was 44,550. Sedimentation rate was 38 mm. per hour. Serological test for syphilis was negative. The urine was normal, the specific gravity varying between 1.020 and 1.025. Radiological examination of the chest was interpreted as diffuse fibrosis with consolidation in the right upper lobe. Stools were negative for ova and parasites.

Duodenal secretions contained no tryptic activity and no lipase, but a normal concentration of amylase. Bromsulfalein retention was 14 per cent. Total serum protein was 8.11 grams per cent. Albumin was 5.11 grams per cent and globulin was 3.0. Thymol turbidity was 5.6 units and cephalin flocculation was 2 plus in forty-eight hours. Serum bilirubin was normal. Total blood fat was 860 mg. per cent. Fatty acids were 749 mg. per cent. Lecithin was 165 mg. per cent. Cholesterol was 111 mg. per cent. Cholesterol esters was 57 mg. per cent. Glucose tolerance tests showed fasting blood sugar of 48.0 mg. per cent, one-half hour 92.4, one hour 149, two hours 110, three hours 53.5. Three minims of 1:1,000 Adrenalin at this point was not followed by an increase in blood sugar, even when repeated. Radiological examination of the gastrointestinal tract was normal. The skeletal survey was negative. Stool fat and nitrogen output were approximately twice normal. There were five circulating eosinophiles per cubic millimeter before and after a test dose of Adrenalin.

On Nov. 8, 1950, the administration of cortisone was begun, in a dosage of 200 mg. for two days and 100 mg. each twenty-four hours thereafter for ten days. Stool nitrogen and fat was proportional to intake and was not altered by therapy. Excretion of 17-ketosteroids increased from 3.5 to 10.5 mg. per twenty-four hours during the period of cortisone administration.

Balance Studies.—While receiving cortisone the child's appetite spontaneously increased until he doubled his

TABLE IV. METABOLIC CHANGES FROM CORTISONE THERAPY FREE DIET, UNLIMITED INTAKE. AVERAGE DAILY BALANCES OF ELECTROLYTES AND NITROGEN

Base Line Studies

STUDY DAYS	CALORIES PER 24 HOURS	NITROGEN (GM.) IN	OUT	BAL.
1-3	1,618	13.11	12.26	0.85
Total				2.55

Nitrogen gain for study period 2.55 grams × 29.2 = 73 grams protoplasm

Biliary Cirrhosis—Cortisone Therapy Started

STUDY DAYS	CALORIES PER 24 HR.	NITROGEN (GM.) IN	OUT	BAL.	SODIUM (mM) IN	OUT	BAL.	POTASSIUM (mM) IN	OUT	BAL.	CORTISONE MG./DAY
1-3	2,336	16.90	8.79	8.11	90	63	27	83	91	–8	165
4-6	2,276	15.33	10.39	4.94	88	77	11	87	85	2	100
7-9	3,794	24.83	17.44	7.39	179	80	99	144	118	26	100
10-12	3,465	20.07	15.22	4.85	154	83	71	124	108	16	100
Total				75.87			624			108	1,400

Nitrogen gain 75.87 grams × 29.2 = 2,215.4 grams protoplasm
Sodium gain 624 mM ÷ 151 × 1,000 = 4,132 grams – 380 (76 × 5) = 3,752 grams extracellular fluid
Potassium gain 108 mM ÷ 143 × 1,000 = 755 grams – 1,444 (76 × 19) = –689 grams intracellular fluid
Theoretical weight gain 5,278.4 grams
Actual weight gain 5,897 grams
Caloric discrepancy 618.6 grams error, fat or water

Profuse diuresis produced by Salyrgan Theophylline. Patient lost 4,083 grams of weight, 45.0 grams of nitrogen, 495 mM of sodium, and 20 mM of potassium previously stored.

13-16	2,193	13.33	23.35	–10.02	61	154	–93	70	93	–23	
17-19	2,337	14.66	16.31	– 1.65	60	101	–41	52	28	24	
Grand total for study				30.84			129			88	

Nitrogen gain for study period 30.84 grams × 29.2 = 900.5 grams protoplasm
Sodium gain 129 mM ÷ 151 × 1,000 = 854 grams – 155 (31 × 5) = 699 grams extracellular fluid
Potassium gain 88 mM ÷ 143 × 1,000 = 615 grams – 589 (31 × 19) = 26 grams intracellular fluid
Theoretical weight gain 1,625.5 grams
Actual weight gain 1,814 grams
Caloric discrepancy 188.5 grams error, fat or water

Patient W. K. Aged 11 years. Height 131 cm. Weight at start of study 21,772 grams
Weight at end of study 23,586 grams
Basal caloric requirements 1,025
Total caloric intake above requirements 12,446

calorie intake. Following the completion of therapy he was given a diuretic in the form of Salyrgan Theophylline which was followed by a profuse diuresis. The results of the balance studies are summarized in Table IV.

Approximately a month after discharge from the hospital this patient developed right heart failure and expired. Autopsy examination revealed biliary cirrhosis, cystic fibrosis of the pancreas, bronchiectasis, and multiple lung abscesses.

DISCUSSION

The patients on whom these studies were conducted are in themselves of interest. The two children with rheumatoid arthritis illustrate the necessity for considering this diagnosis in preschool children when searching for the causes of obscure fever after exhaustive negative clinical and laboratory investigations. Although we know of no way to actually establish this diagnosis before the appearance of typical joint changes, the presence of a persistently elevated sedimentation rate, transient nondescript erythemas, generalized lymphadenopathy of varying degree, splenomegaly, anemia, and fever out of proportion to other evidences of disease provide supporting evidence. One patient followed in this clinic had cyclic fever from the age of 5 months to 5 years before joint changes occurred. In our experience aureomycin not uncommonly controls the fever in patients with early Still's disease and may occasionally produce a remission, perhaps by the antibiotic removal of foci of infection. Freyberg[4] states that the dosage of ACTH or cortisone required for children may be as great as in adults and that it depends more on the severity of the disease than on the factor of body size. He also warned that the metabolic and endocrine complications may be greater in the child because of the larger ratio between hormone dose and body size. These cases confirm his observations since the amount of cortisone required to control symptoms resulted in rapid metabolic changes and the development of a partial Cushing's syndrome after ten days of therapy. Dangerous metabolic alterations are not common when cortisone is given for less than ten days. Although the antirheumatic and antipyretic effects of cortisone are quite constant the clinical pattern following the withdrawal of therapy varies not only from patient to patient but also in the reaction of the same patient following successive courses of therapy. When the administration of cortisone is discontinued the patient may remain in remission for a time or have a relapse with a recurrence of symptoms of either greater or lesser intensity than those existing prior to treatment. The response to therapy seems to be more satisfactory when the rheumatoid process is very acute. Case 1 is actually worse after several courses of therapy. Case 2 seems to have been improved.

The patient with cystic fibrosis of the pancreas is one of the oldest ever reported. His course illustrates the natural history of this disease and the relationship between the pathological changes in the pancreas, the liver, and the lungs. This patient was certainly not improved by cortisone therapy and the spread of his pulmonary infection may have been enhanced.

Even before cortisone became available Albright[5] had predicted its anti-

anabolic effect and its effect on the body stores of sodium, potassium, and chloride.

A negative nitrogen balance results from the administration of ACTH or cortisone in large doses, whether the nitrogen intake is high or low. In clinical practice the antipyretic and antirheumatic effects of these substances may often be obtained with amounts which do not produce such biochemical aberrations. Our data indicate that the antianabolic effect of cortisone is to some extent neutralized by increased appetite. When the diet of a patient receiving cortisone is quantitatively limited, nitrogen excretion increases until balance is re-established at a level corresponding to nitrogen intake (Table I). If the dose of cortisone is sufficiently large it may actually produce a negative nitrogen balance. A marked increase in appetite is usually noticeable from forty-eight to seventy-two hours after the administration of cortisone is begun. Caloric and nitrogen intake increases rapidly thereafter, and if the diet is not restricted the caloric intake may reach levels five times as great as the patient's basal caloric energy requirement. The associated increased nitrogen intake may then be greater than nitrogen excretion even when the latter is augmented by the antianabolic effect of cortisone. The data in Table II illustrate this sequence of events. This patient was allowed to eat as much as he wished. His basal caloric requirement for height and weight at 4 years of age was 800 calories. His caloric intake increased from 1,677 to 3,752 calories per twenty-four hours. This child ate as many as eight eggs for breakfast in addition to several helpings of cereal, milk, toast, fruit juice, etc. Although his nitrogen excretion increased from 6.56 to 13 grams per day, his nitrogen intake increased more rapidly, approaching 20 grams per twenty-four hours, with the patient storing as much as 6 grams of nitrogen per day. If cortisone were continued nitrogen excretion would probably eventually equal or exceed nitrogen intake since there seems to be a ceiling beyond which more food cannot be consumed. In practice the weight gain of these patients may be so rapid and so extreme that therapy must be discontinued. Between the third and the fifteenth day of therapy this patient gained a pound a day. He developed a partial Cushing's syndrome and pronounced enlargement of the liver. Liver function tests became mildly abnormal. Hypertension was also evident. For these reasons the treatment program of cortisone plus free dietary intake had to be discontinued. When the same patient was retreated one month later his diet was limited to 1,900 calories. Although approximately the same amount of cortisone was given over the same period of time his weight gain was only half that during the first course of therapy (Table III).

The increase of appetite resulting from cortisone therapy persists from days to weeks after the steroid is discontinued. During this period before the appetite returns to normal and nitrogen equilibrium is re-established at a lower level, these patients retain relatively large amounts of nitrogen. This is true even when dietary intake is limited (Tables I and III). Intermittent courses of cortisone therapy may therefore result in an over-all nutritional gain (Figs. 4 and 5).

Table IV would indicate that nitrogen assimilation may not be directly proportional to nitrogen retention while cortisone is actually being administered since a mercurial-produced diuresis resulted in a loss of approximately half of the nitrogen the patient had retained. An alternative explanation in this patient is that his liver disease interfered with protein synthesis. Unfortunately, determinations of blood amino acid nitrogen were not done on this patient.

The effect of cortisone therapy on the retention of sodium, potassium, chloride, and water is more variable and less predictable. For the two patients whose diet was limited the proportion of weight gain due to electrolyte and water retention was 29 per cent (Table I) and 35 per cent (Table III). The partition between intra- and extracellular fluid was not, however, the same, being 25 per cent extracellular fluid in the first study and 64 per cent extracellular fluid in the second study. When the diet is unlimited electrolyte and water retention is of a greater order of magnitude, both relative and absolute. Sixty-eight per cent of the weight gain for the patient with rheumatoid arthritis

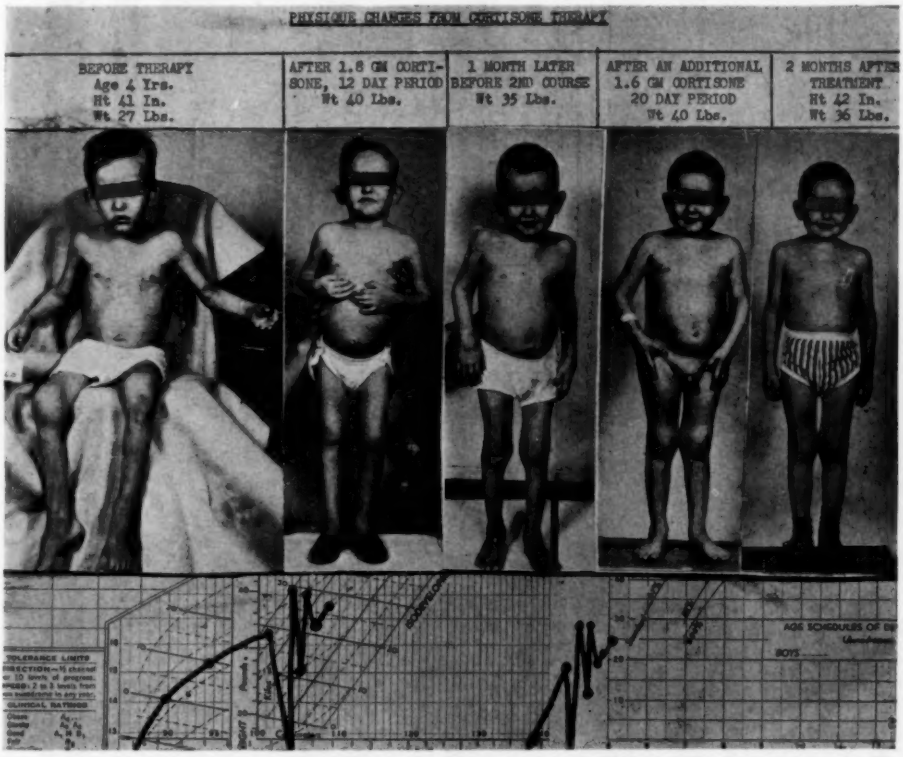

PHYSIQUE CHANGES FROM CORTISONE THERAPY
BEFORE THERAPY
Age 4 Yrs.
Ht 41 In.
Wt 27 Lbs.
AFTER 1.6 GM CORTISONE, 12 DAY PERIOD
Wt 40 Lbs.
1 MONTH LATER BEFORE 2ND COURSE
Wt 35 Lbs.
AFTER AN ADDITIONAL 1.6 GM CORTISONE 20 DAY PERIOD
Wt 40 Lbs.
2 MONTHS AFTER TREATMENT
Ht 42 In.
Wt 36 Lbs.

Fig. 4.

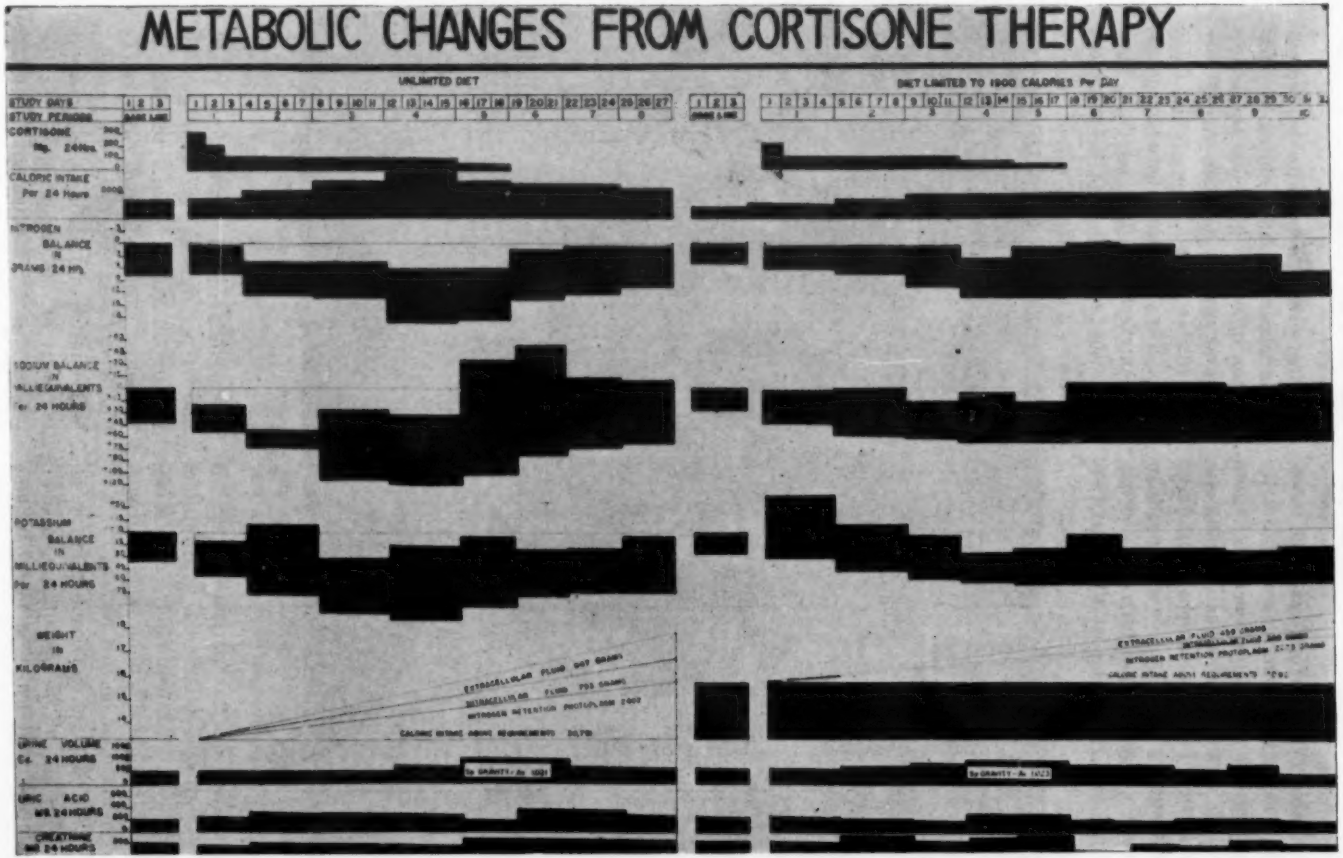


Fig. 5.—Graphic representations of balance studies corresponding to photographs in Fig. 4.

(Case 2) resulted from electrolyte and water retention. The partition between intracellular and extracellular fluid gain was approximately equal (Table II). The patient with biliary cirrhosis retained even more fluid. Before the diuretic was given, 71 per cent of the very marked weight gain was due primarily to sodium retention. Potassium retention was even more inhibited than nitrogen assimilation in this patient (Table IV). In any case, weight gain from electrolyte and water retention is lost within a few days after the cessation of therapy. There are also wide fluctuations during therapy.

The natural reaction of the homeostatic mechanism, when subjected to large doses of cortisone, is a marked bulimia and a concomitant increase in caloric, nitrogen, electrolyte and water intake, thus neutralizing to some extent the antianabolic and hypokalemic effects of the steroid, preserving normal serum levels. The excessive intake of potassium and nitrogen is desirable, but the retention of sodium and chloride and the increase in extracellular fluid resulting therefrom may produce undesirable weight gain and edema necessitating cessation of therapy. Since excessive intake on a free diet magnifies these distortions it would seem advisable to limit the diet quantitatively to approximately 30 per cent above requirements if therapy is to be long continued. This diet should be as sodium free as possible. The addition of potassium is not necessary if food intake is adequate, but may facilitate the storage of nitrogen.[6] The evidence in Table IV suggests that salt limitation is preferable to the use of diuretics since the latter may interfere with nitrogen and potassium assimilation.

These studies suggest that although cortisone is antianabolic if given over extended periods, it may result in over-all nutritional gain when given for ten days or less. When this effect is desired nitrogen retention would result from short, intermittent periods of therapy, the patient being offered a quantitatively unlimited sodium-free diet.

We have attempted to adapt these principles and procedures to the treatment of nutritional failure. Infants who had no specific detectable organic reasons for growth failure were given ACTH or cortisone for five-day periods. The results were rather erratic. The effect of cortisone on appetite is not as constant in infants as in older children. There is no demonstrable effect on the appetite of newborn infants. Since food tolerance is also usually reduced in infants with marasmus, increased intake may result in diarrhea. Several infants between 6 and 12 months of age did exhibit increased appetite and sudden reversal of nutritional failure when given ACTH for short periods. In these infants growth once being resumed was sustained and recovery from growth failure occurred after ACTH was discontinued.

SUMMARY AND CONCLUSIONS

1. Two 4-year-old white males, both of whom had juvenile rheumatoid arthritis, were treated with cortisone. The clinical response in both cases was similar to those originally reported by Hench, Kendall, Slocumb, and Polley.[1] One of these patients stayed in remission after two courses of therapy. The

other actually became worse. This patient responded almost as well to aureomycin as to cortisone, perhaps by antibiotic removal of foci of infection.

2. An 11-year-old white male with cystic fibrosis of the pancreas and biliary cirrhosis was also treated with cortisone. Although this patient improved during therapy his pulmonary infection was more severe after the withdrawal of cortisone.

3. Changes in sedimentation rate, blood counts, body weight, blood pressure, glucose tolerance, eosinophile response to Adrenalin, serum electrolytes, serum protein, urinary creatinine, and urinary uric acid are consistent with those previously reported by others. Urine chloride approximately balanced the sum of urine sodium and potassium.

4. Minor abnormalities of cephalin flocculation, thymol turbidity, and bromsulfalein excretion were noted during the course of cortisone therapy.

5. Excretion of 17-ketosteroids increased slightly during cortisone therapy. Since basal excretion levels of 17-ketosteroids are low in this age group these determinations probably represent the excretion of metabolic products of cortisone.

6. Observations are reported on four studies of nitrogen, sodium, and potassium balances during cortisone therapy. In two of the studies the dietary intake was limited to 1,900 calories per twenty-four hours. In the other two studies the patients were offered a quantitatively free diet and allowed to consume as much as desired.

7. From forty-eight to seventy-two hours after cortisone is started most children exhibit a marked increase in appetite. If the diet is not restricted their caloric intake may be four or five times their basal requirement.

8. Although cortisone is antianabolic this effect is neutralized by the increased intake of calories, nitrogen, and electrolytes when therapy is continued for ten days or less.

9. Under such circumstances approximately half the weight gain produced is due to nitrogen retention and actual nutritional gain.

10. Undesirable excessive weight gain and edema may be reduced by the use of a salt-free diet. If dietary intake is adequate additional potassium is not required to prevent hypokalemia and potassium deficit, but its use may facilitate nitrogen assimilation.

REFERENCES

1. Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F.: The Effects of Cortone Acetate and Pituitary ACTH on Rheumatoid Arthritis, Rheumatic Fever and Certain Other Conditions, A Study in Clinical Physiology, Arch. Int. Med. **85**: 545, 1950.
2. Reifenstein, C., Albright, F., and Wells, Shirley L.: The Accumulation, Interpretation, and Presentation of Data Pertaining to Metabolic Balances, Notably Those of Calcium, Phosphorus and Nitrogen, J. Clin. Endocrinol. **5**: 367, 1945.
3. Fitch, D. R., Warter, P. J., and Seifter, J.: Preliminary Observations on the Permeability of Human Synoviae and the Relationship to the Treatment of Arthritis. Amer. College of Physicians, Eastern Pennsylvania Round-up, Philadelphia, Jan. 20, 1950.
4. Freyberg, R. H.: The Effects of Cortisone and ACTH in Rheumatoid Arthritis (Panel Discussion), Bull. New York Acad. Med. **26**: 206, 1950.
5. Albright, F.: Cushing's Syndrome, Harvey Lectures, 38, 123, 1942-43.
6. Whiley, J. F., and Benett, C. C.: Inhibition of Catabolic Effect of ACTH on Nitrogen Metabolism by a High Potassium Diet, Federation Proc. **9**: 134, 1950.

THE ANTITHROMBIN TITER IN CYSTIC FIBROSIS OF THE PANCREAS

A Preliminary Report

Irving Innerfield, M.D.,* Alfred Angrist, M.D.,** and James W. Benjamin, Ph.D.***
New York, N. Y.

IN A classic monograph on cystic fibrosis of the pancreas, Dorothy Andersen stated, "It is the recognition rather than the disease that is unusual."[1] A reliable, easily performed laboratory test should increase the diagnostic accuracy for this disease. We are reporting our experience with a new diagnostic test especially useful in early cases of cystic fibrosis of the pancreas, namely, the determination of the plasma antithrombin titer. In one patient, aged two weeks, the diagnosis was established by observing persistently low plasma antithrombin levels accompanying a suggestive clinical course. This case, verified by autopsy, may represent the earliest correct antemortem diagnosis of cystic fibrosis of the pancreas made on the basis of a specific laboratory test.

This report comprises data accumulated while determining antithrombin titers on several control groups and in thirteen patients with proved cystic fibrosis of the pancreas. In addition, suggestions concerning the natural course of the disease will be discussed, based upon a critical analysis of our findings.

From the Department of Physiology and Pharmacology, New York Medical College, New York, and the Department of Pathology, Queens General Hospital, Jamica, N. Y.

This study was supported in part by a grant from the medical research fund of the New York Medical College.

The thrombin was supplied by the Department of Therapeutic Development of Parke, Davis & Company.

*Instructor in Physiology, New York Medical College.

**Clinical Professor of Pathology, New York Medical College; Pathologist and Director of Laboratories, Queens General Hospital.

***Director, Department of Physiology and Pharmacology.

METHODS

Blood was obtained by venipuncture. Nine volumes of blood were added to one volume of 3.2 per cent sodium citrate. After centrifugation at 2,000 r.p.m. for fifteen minutes, the plasma was carefully removed from the cellular elements and either kept in ice until analyzed or antithrombin determinations were immediately carried out. The normal control plasmas were collected in the same manner.

Preliminary Thrombin Standardization.—Our determinations are a modification of the method of Quick.[2] In this method, Parke-Davis topical thrombin is used.

1. Ten milliliters of sterile isotonic saline are injected into the vial containing 5,000 units of Parke-Davis topical thrombin.
2. Two milliliters of this solution are added to 65 ml. of isotonic saline.
3. One-tenth milliliter of this diluted thrombin solution is added to 0.2 ml. of normal plasma and a clotting time is recorded. If the clotting time obtained is less than 15 seconds, saline solution in 3 c.c. amounts is added and the addition of 0.1 ml. of thrombin to 0.2 ml. of plasma is repeated. When a clotting time in the range 15 to 18 seconds is obtained, the thrombin solution is considered standardized. This standardized preparation must be surrounded by a chilling solution at 4° C.

Antithrombin Titer.—In our test defibrinated plasma is incubated with a standard thrombin solution. Fibrin is subsequently furnished by the addition of normal plasma. The speed with which the defibrinated plasma neutralizes a known quantity of thrombin is a measure of antithrombin activity. The details of this procedure are as follows:

1. To 0.1 ml. of 3.2 per cent citrate 9 ml. of whole blood are added.
2. The citrated blood is centrifuged at 2,000 r.p.m.
3. To 1.0 ml. of citrated plasma 0.4 ml. of standardized thrombin is added.
4. After allowing two to four minutes for a clot to form, this clot is removed (defibrinated).
5. To 0.9 ml. of freshly standardized thrombin solution 0.1 ml. of this defibrinated plasma is added.
6. This solution and a series of 0.2 ml. of normal plasma are then incubated at 37° C.

WATER BATH SET-UP (37° C.)

*.9 △.1	°.2	°.2	°.2

Unknown

*.9 △.1	°.2	°.2	°.2

Normal Control

*—Thrombin.
△—Defibrinated plasma.
°—Normal plasma.

7. At intervals of one, three, five, ten, fifteen, twenty, and twenty-five minutes, 0.1 ml. of the incubated solution is added to 0.2 ml. of normal plasma and a clotting time is taken. A normal control is run with, and five minutes following, the final completion of each unknown determination. Defibrinated plasma from normal persons is incubated with the standard thrombin for use in the control procedures. A "normal" result is recorded when the clotting times of the control and unknown samples are either identical, or show minimal variation. An "elevated" titer is recorded when the clotting time of the unknown samples is at least 100 per cent greater than those of the controls. A low titer is recorded when the clotting time of the unknown sample is 100 per cent less than those of the controls in five- and ten-minute samples.

Antithrombin Titer Following Pancreatic Stimulation (Urecholine).—In three patients having cystic fibrosis of the pancreas (above the age of 3 years), a subcutaneous dose of Urecholine (0.5 mg.) was given followed by four half-hour determinations of antithrombin titers. Ten normal control patients were given similar doses of Urecholine, followed by antithrombin titer determinations. These ten control patients will be referred to as "Urecholine control patients" to avoid confusion with the other control group.

Duodenal Juice Trypsin Determinations.—The viscosimetric method of Northrup and Hussey, as modified by Andersen, was employed.[3]

SELECTION OF PATIENTS

The patients were between the ages of 1 day and 7 years. Five groups of subjects are included in the present report:

1. Seventy-five normal infants and children.
2. Twenty-two infants and children with chronic diarrhea.
3. Two infants with idiopathic steatorrhea.
4. Three marasmic infants.
5. Thirteen infants with cystic fibrosis of the pancreas.

The following criteria were used in establishing the control group (seventy-

five patients): all were of normal weight and physical development and were gaining weight at the time of the examination. Children with histories of prolonged bouts of diarrhea or other gastrointestinal or nutritional disturbances were exeluded. Most of the patients in this group were obtained from a well-baby clinic. The hospital cases consisted of the following diagnoses: virus pneumonia, recovered; congenital heart disease without decompensation; benign tumors; mental defectives; chronic eczematoid dermatoses; behavior problems, and thirty-five newborn normal infants between 1 and 8 days old.

Three patients were marasmic. Each was at first thought to have cystic fibrosis of the pancreas because of prolonged diarrhea and inanition.

For the data on six patients with proved cystic fibrosis of the pancreas we are indebted to Dr. Dorothy Andersen of Babies Hospital. One case, proved by autopsy, is from Harlem Hospital. The remaining six cases came from our own and affiliated institutions through the courtesy of Dr. Lawrence B. Slobody, Director of Pediatrics. Twelve of the cystic fibrosis patients are living. Five are doing well under careful treatment, three are doing fairly well, and four have severe respiratory infections.

TABLE I. ANTITHROMBIN TITER, TRYPSIN LEVELS AND STOOL FAT IN TWO PATIENTS WITH IDIOPATHIC STEATORRHEA

	AGE	ANTITHROMBIN TITER	TRYPSIN	STOOL FAT (% DRIED WT.)
R. G.	14 mo.	normal range	212	37.7
L. T.	19 mo.	normal range	198	33.4
Normal	1-2 yr.	normal range	241	10-25
Diarrhea	1-2 yr.	normal range	181	10-20

TABLE II. TRYPSIN LEVELS IN THREE PATIENTS WITH MARASMUS FROM PROLONGED DIARRHEA

	AGE MONTHS	WEIGHT KG.	TRYPSIN
C. R.	6	5.78	44
B. L.	10	6.14	29
R. T.	3	3.87	37
Fibrosis of the pancreas maximum values			8

The group with diarrhea was composed of twenty-two infants and children with histories of prolonged, recurrent bouts of diarrhea either at the time of examination or the latest episode within one month of study. No instances of infection with the dysentery groups are included in this group. None of these patients showed evidence of iodiopathic steatorrhea.

Two patients had classic idiopathic steatorrhea. Each had elevated fat content of the stool and was on normal diets.

RESULTS

No significant elevations or depressions in plasma antithrombin levels were observed in any of the control groups. The trypsin levels were normal in the first three control groups, but were severely depressed in the marasmic infants.

In the patients with cystic fibrosis of the pancreas extremely low antithrombin titers were obtained in baby P. K., aged 3 weeks. Patient G. A., aged 7 months, patient L. B., aged 5 months,

and patient R. V., aged 9 months showed markedly elevated titers of antithrombin. In the remaining nine patients, each older than 3 years, the antithrombin titers were normal. Following Urecholine stimulation in three older patients with cystic fibrosis of the pancreas, two showed a rise in antithrombin titer. None of the ten Urecholine normal control patients showed elevated antithrombin titers following Urecholine stimulation. In twelve of of the thirteen patients with cystic fibrosis of the pancreas, trypsin levels were zero or slightly above (Table III). Trypsin levels were not determined on baby K.

we have described animal experiments suggesting a direct relationship between trypsin levels and plasma antithrombin titers.[4] In fifty of fifty-five patients known to have increased trypsin levels (proved acute pancreatitis), we observed distinctly elevated plasma antithrombin titers throughout the course of the acute illness. On the basis of this work we became interested in the antithrombin titer in cases characterized by decreased trypsin levels.

The 3-week-old baby (P. K.) had consistently low antithrombin leve's. The ante-mortem diagnosis of congenital pancreatic deficiency was verified

TABLE III. DUODENAL JUICE TRYPSIN IN CONTROL GROUPS

AGE CONTROLS	NUMBER	TRYPSIN UNITS PER C.C.
0-2 mo.	42	Mean 152.3
2-6 mo.	11	150.6
6-12 mo.	14	187.1
1-2 yr.	21	212.0
2-7 fr.	11	187.0

AGE PANCREATIC FIBROSIS	NUMBER	TRYPSIN UNITS PER C.C.
3 wk.	1	Not performed
5 mo.	1	0
7 mo.	1	0
9 mo.	1	0
31 mo.	1	0
34 mo.	1	1
40 mo.	1	6
46 mo.	1	2
56 mo.	1	6
62 mo.	1	0
67 mo.	1	0
72 mo.	1	8
82 mo.	1	0

DISCUSSION

A sine qua non of congenital pancreatic deficiency is absent or markedly diminished trypsin activity. Since the assay of trypsin levels in the duodenal juice is a cumbersome procedure, an improved method for determining trypsin activity has been the subject of considerable study. In previous reports

at autopsy. This significant development suggests the feasibility of antithrombin titer determinations throughout the period when a diagnosis of pancreatic involvement is most difficult to establish, namely, the first few days and weeks of life. In each of thirty-five normal infants, aged 1 to 28 days, normal antithrombin titers were

obtained. Depressed antithrombin titers (baby P. K.) are, therefore, abnormal in the newborn infant and imply faulty trypsin activation.

REPORT OF CASE.—A negro boy was born at Harlem Hospital on March 11, 1951. The period of pregnancy was normal, and there was no history of maternal syphilis. There was a low forceps delivery after a labor of sixteen hours. The baby weighed 5 pounds, 9 ounces, and did well the first twenty-four hours. The next morning the infant vomited dark brownish green mucus. Feedings were taken poorly. No meconium was passed. The second day the abdomen became considerably distended. Widened loops of intestine were visible through the anterior abdominal wall. The child's condition was poor; he refused feedings, the vomiting became projectile, and the abdominal distention was worse. A diagnosis of intestinal obstruction possibly due to intestinal atresia, meconium ileus, or intussusception was made and an exploratory laparotomy was performed. At operation nothing was found except greatly dilated loops of bowel. The postoperative impression was that of a spontaneously corrected volvulus or intussusception.

Following operation, the infant did fairly well for several days. Stools were light colored and infrequent. On the fourteenth day, however, vomiting recurred and abdominal distention was again observed. The possibility of congenital pancreatic deficiency was raised, and a plasma antithrombin test was performed. The results were as follows:

Incubation Period (Minutes)	*Control (Sample clotting time) (Defibrinated plasma and thrombin)*	*Baby P. K. (Clotting time) (Defibrinated plasma and thrombin)*
1	17	11
5	28	13
10	57	17
15	94	20
20	178	26
25	5 min.	34

The extremely low plasma antithrombin titer of baby P. K. as compared to the normal control was considered compatible with lack of trypsin activation and consistent with the diagnosis of fibrocystic disease of the pancreas.

The infant continued to do poorly, and expired two days after the antithrombin test was performed.

The essential pathologic changes noted at autopsy were limited to the gastrointestinal tract and the pancreas.

The duodenum was slightly dilated. The jejunum became progressively more dilated, and two greatly distended loops were found in the proximal portions of the ileum. These loops were filled with thick, mucoid, yellowish, sticky material. The ascending, transverse, and descending portions of the colon were smaller in diameter than the terminal ileum. There was no evidence of inspissated meconium.

The pancreas occupied its usual position and appeared small, flabby, and its lobulations seemed smoother and rounder than usual. A distinct area of constriction without band formation was present in the region of the glandular neck. The main pancreatic duct was followed for about 10 mm. then terminated blindly.

Histologically (Figs. 1 to 4), the pancreas showed many areas of interlobular and intralobular fibrosis. Perilobular bundles of connective tissue were present, composed of a fine fibrillar network containing several fibroblasts. An occasional lymphocyte was seen, but there was nowhere any accumulation of acute inflammatory cells. The histologic appearance was not thought to be that of inflammatory fibrosis.

In one section a large excretory duct was found, containing many proliferating ductules.

Although the acini were abundant, their structure was not normal. The component epithelial cells showed disorderly arrangement. The epithelium was hyperplastic in several acini, causing considerable narrowing of the lumen. Irregular groups of epithelial cells grew like buds into a loose and

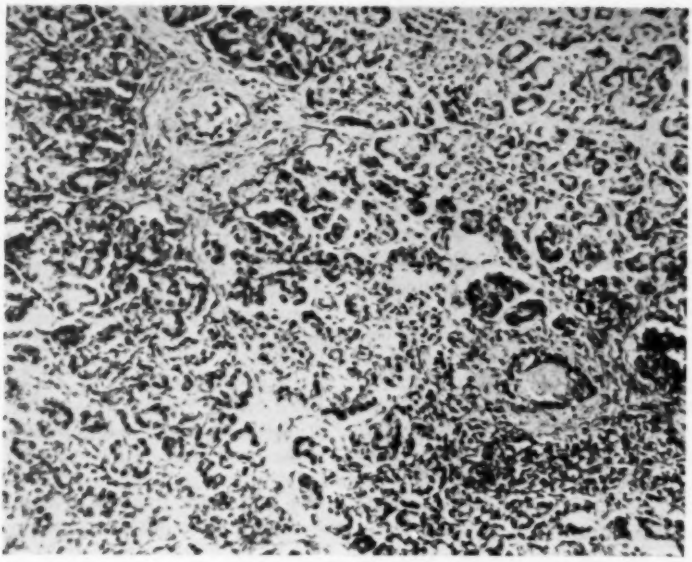


Fig. 1.—Photomicrograph of a section of the pancreas showing dense inspissated eosinophilic material in a duct. See duct in lower right. Note increase in connective tissue and disorderly arrangement of the epithelial elements in the lobules.

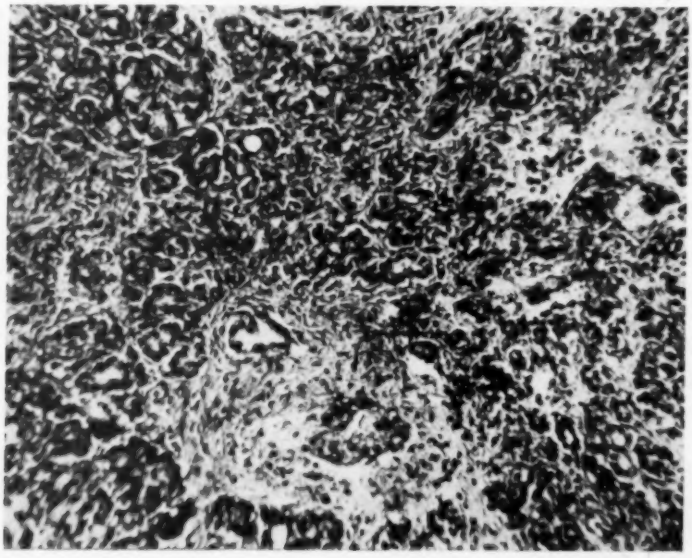


Fig. 2.—Low-power photomicrograph showing two pancreatic ducts embedded in a dense connective tissue stroma. One of the ducts show almost complete obliteration due to epithelial hyperplasia and inspissation of eosinophilic material.

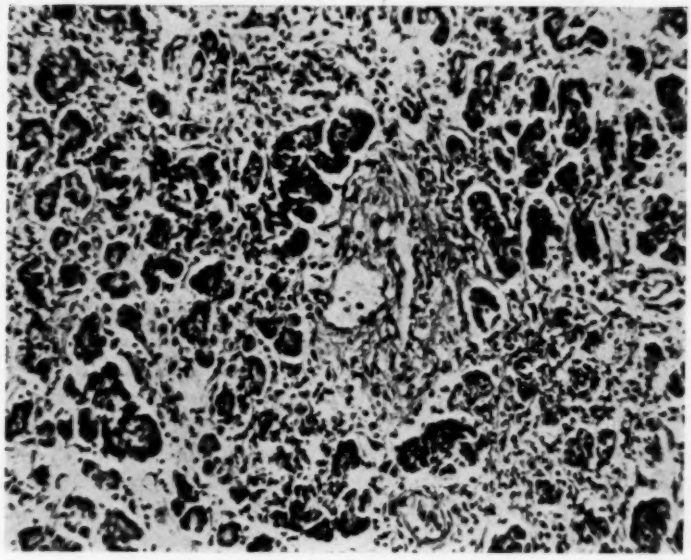


Fig. 3.—Low-power photomicrograph showing loose fibrous tissue separating tubular and acinar structures. There is evidence of abortive attempts of epithelial elements to form acini.

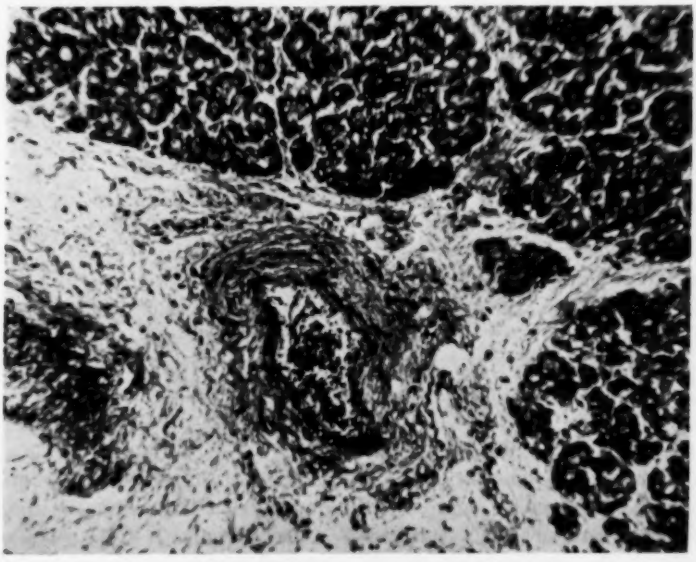


Fig. 4.—High-power photomicrograph through the main pancreatic duct showing extensive periductal fibrosis with considerable cellular debris in the lumen.

delicate meshwork of connective tissue fibrils.

The histologic impression was that of faulty development of the pancreatic acini, with interference with normal maturation of the ductules into acini.

The islets of Langerhans were abundant and normal.

were done on several infants of similar age range (5 to 10 months) and an additional control group consisted of three marasmic infants. In each of the controls the antithrombin titer was normal.

LEVELS OF ANTITHROMBIN TITER AND DUODENAL JUICE TRYPSIN IN PATIENTS WITH CONGENITAL PANCREATIC DEFICIENCY.

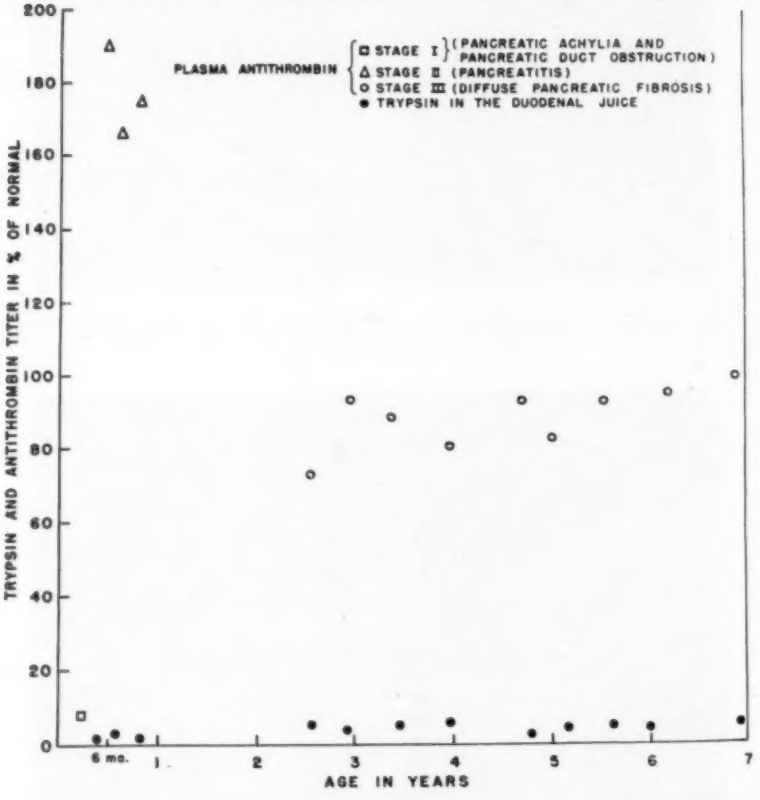


Fig. 5.

The plasmas of patients G. A., aged 7 months, L. B., aged 5 months, and R. V., aged 9 months (Fig. 5) yielded extremely high antithrombin titers. This significant finding is discussed below. Control antithrombin studies

The antithrombin titers were either normal or "low normal" in the nine older patients (2 to 7 years) having proved cystic fibrosis of the pancreas (Fig. 5). Three patients in this group received 0.1 mg. of Urecholine sub-

cutaneously prior to antithrombin titer determinations. We have reason to believe that patients with pancreatic insufficiency in a stage of remission may show elevated antithrombin titers following parasympathetic stimulation. In one patient the response to Urecholine was characterized by a prompt sustained elevation in antithrombin. In another only a delayed, brief period of antithrombin elevation was noted. No response occurred in the third patient. In a control series (ten patients), antithrombin elevations did not occur following Urecholine. Further investigation of antithrombin titers following Urecholine stimulation seems justified.

Appraisal of the observed alterations in antithrombin titer in proved fibrocystic disease of the pancreas indicates that the titers seem to follow three patterns correlated with the age of the patient, total duration of the illness, and the particular stage in the natural course of the illness.

Stage I: The Pattern of Pancreatic Duct System Atresia and Low Antithrombin Titer.—Baby P. K., previously discussed, typifies the major findings of this stage. Antithrombin titers are extremely low, indicating low trypsin levels. Acinar atrophy and fibrosis (Figs. 1 to 4) plus hyperplasia of the pancreatic duct epithelium are present. Patients with severe forms of this disease usually succumb after a few days or weeks.

Stage II: The Pattern of Interstitial Pancreatitis and High Antithrombin Titers.—Three patients, G. A., L. B., and R. V., each less than 1 year old, had high titers of antithrombin. It is postulated that these patients survived a preliminary stage of incomplete pancreatic duct obstruction and temporarily adapted their digestive processes to diminished external pancreatic secretion. The combined effects of partial pancreatic duct obstruction with vagal and humoral pancreatic stimulation following food intake produced enzyme overflow into the surrounding parenchyma, with resultant interstitial pancreatitis. We observed peak antithrombin titers in 91.4 per cent of proved cases of acute pancreatitis.[4, 5] The elevations in antithrombin titer observed in the above three patients were in the range associated with pancreatitis.

Stage III: The Pattern of Fibrocystic Disease of the Pancreas and Normal Antithrombin Titer.—The nine children in the 2- to 7-year-old group presented the classic nutritional and respiratory components of the fully developed disease. The pancreas is now a homogenous mass of contracted fibrous tissue practically devoid of functioning acini, in the healed, scarred, irreversible stage following diffuse pancreatitis. The normal to "low normal" antithrombin titers observed at this stage reflects the exquisite sensitivity of antithrombin to minute quantities of trypsin generated from a few feebly functioning foci of pancreatic acini. It is conceivable that in total pancreatic fibrosis there would be concomitant depression in antithrombin titer.

Table IV illustrates the natural course of cystic fibrosis of the pancreas, suggested by data revealed in this paper. The prognosis in any of the three stages is influenced by many variables, including the degree of pancreatic duct atresia and obstruction, the extent of pancreatic parenchymal involvement, the quantity of formed pancreatic enzymes actually transported to the

TABLE IV. THE SUGGESTED NATURAL COURSE OF CONGENITAL PANCREATIC DEFICIENCY

STAGES OF THE DISEASE	AGE OF PATIENT	DEGREE OF PANCREATIC DUCT OBSTRUCTION	ACINAR TISSUE CHANGES	ANTITHROMBIN TITER	DUODENAL JUICE TRYPSIN	USUAL OUTCOME
I The stage of pancreatic achylia and pancreatic duct obstruction	One day to few months	Complete	Usually extensive	Very low	Absent	Death within the first few days or weeks.
		Incomplete	Moderate to minimal	?	Low	Survive Stage I. Often unrecognized.
II The stage of interstitial pancreatitis	Few months to 1-1½ years	Complete	Extensive	Very high	Absent	May die in this stage; develop respiratory infections early; bulky stools; weight loss; marasmic.
		Incomplete	Extensive, moderate or minimal	High	Low or absent	Usually survive this stage; course less stormy; less weight loss; later developement of respiratory infections.
III The stage of diffuse pancreatic fibrosis and acinar atrophy	Older than 1-1½ years	Complete	Extensive fibrosis, few foci of functioning acini	Low normal	Absent	Full-blown classical clinical picture of cystic fibrosis; death from respiratory infection within few years.
		Incomplete	Moderate fibrosis, foci of functioning acini	normal	Low or absent	Milder symptoms of pancreatic insufficiency; greater life expectancy; may respond fairly well to treatment for celliac syndrome.

duodenum, and the over-all nutritional status.

It is interesting to compare direct duodenal juice analysis with plasma antithrombin titer determinations as estimates of trypsin concentration.

Antithrombin titers represent a highly sensitive plasma response to the formation of trypsin in the pancreas.

Direct duodenal juice analysis estimates the quantity of trypsin reaching the duodenum. The tests supplement one another in that antithrombin titer quantitates acinar activity (trypsin production factor); duodenal juice trypsin quantitates the formed trypsin entering the duodenum (pancreatic duct obstruction factor).

SUMMARY

The plasma antithrombin titer was determined in 102 control patients, and in thirteen patients having proved cystic fibrosis of the pancreas. In none of the patients comprising the control groups was the plasma antithrombin elevated or diminished. In a 3-week-old infant dying of cystic fibrosis of the pancreas, however, the plasma antithrombin titer was exceedingly low. In three infants, less than 1 year old, having cystic fibrosis of the pancreas, the antithrombin titers were strikingly high. In each of the remaining nine patients comprising the older age group of cystic fibrosis patients (2 to 7 years) no marked eleva-

tion or depression in plasma antithrombrin titer was noted.

A critical analysis of these data suggests that the natural course of cystic fibrosis of the pancreas is separable into three periods or stages: a first stage of pancreatic duct atresia and/or obstruction varying from complete to incomplete, with or without extensive parenchymal damage. This stage occupies the first days or weeks of life. In survivors, a second stage develops within weeks or months, characterized by interstitial pancreatitis secondary to the extravasation of obstructed pancreatic enzymes. A third stage, the stage of pancreatic contraction and scarring, follows and is characterized by extensive parenchymal replacement fibrosis, areas of hyaline degeneration, the appearance of corpora amylacea, the development of large cysts, and other histologic phenomena associated with cystic pancreatic fibrosis in its end stage.

Characteristic levels of plasma antithrombin titers are correlated with each of these three stages. Antithrombin titers of diagnostic range are obtainable during the first and second stages of congenital pancreatic deficiency. In Stage III the antithrombin titer is normal. In two of three patients in Stage III, however, elevated antithrombin titers followed Urecholine stimulation.

REFERENCES

1. Anderson, D. H.: Cystic Fibrosis of the Pancreas, Vitamin A Deficiency and Bronchiectasis. J. PEDIAT. 15: 763, 1939.
2. Quick, A. J.: The Normal Antithrombin of the Blood and Its Relation to Heparin. Am. J. Physiol. 123: 712, 1938.
3. Andersen, D. H., and Early, M. V.: Method of Assaying Trypsin Suitable for Routine Use in the Diagnosis of Congenital Pancreatic Deficiency. Am. J. Dis. Child. 63: 891, 1942.
4. Innerfield, I., Angrist, A., and Benjamin, J. W.: The Antithrombin Titer in Acute Pancreatitis. Bull. New York Acad. Med. 27: 399, 1951.
5 Idem: Am. J. Med., To be published.

HERPES SIMPLEX ENCEPHALITIS

DAVID R. GINDER, M.D., AND C. MERRILL WHORTON, M.D.*
ATLANTA, GA.

CENTRAL nervous system disease caused by herpes simplex virus is rarely observed in man despite the frequency of herpetic infections and the neurotropic qualities of the virus in experimental animals. Only four cases of acute fatal encephalitis have been reported in which herpes simplex virus was isolated from brains showing histologic signs of encephalitis and acidophilic intranuclear inclusion bodies.[1, 2, 3] In addition, herpes simplex virus has been isolated from the cerebrospinal fluid of several patients who had nonfatal illnesses characterized by signs and symptoms of meningo-encephalitis.[4, 5, 6]

A recently studied fatal case of herpes simplex encephalitis is reported here. A strain of herpes simplex virus was isolated from the brain in which eosinophilic intranuclear inclusions were demonstrated.

CASE REPORT

A 22-month-old white male child was admitted to the hospital shortly after the onset of a generalized convulsion. The illness began Oct. 13, 1949, four days before admission, with fever and restlessness that persisted until admission. Except for vomiting that preceded the convulsion no other signs of illness had been detected. The infant's mother was subject to recurrent herpes labialis. However, she had not had an attack in the three to four months immediately prior to the patient's illness. The patient had had neither stomatitis nor herpes labialis. Physical examination on admission revealed a slightly lethargic infant with a rectal temperature of 101.4° F. and a pulse rate of 162. There were no herpes labialis or other mucocutaneous lesions. The neck was supple. The neurological findings were within normal limits. Examination of the blood revealed 12.9 Gm. of hemoglobin per 100 mm. and 9,050 white blood cells per cubic millimeter of which 86 per cent were polymorphonuclear leucocytes. The blood Kahn test was negative. Urinalysis revealed no abnormalities. Lumbar puncture on the first hospital day revealed clear cerebrospinal fluid with normal pressure. The cerebrospinal fluid contained 90 white blood cells per cubic millimeter of which 20 per cent were polymorphonuclear leucocytes and 80 per cent were lymphocytes, a total protein of 28 mg. per 100 mm., and a sugar concentration of 105 mg. per 100 mm. Bacteriologic cultures of the cerebrospinal fluid showed no growth. Three subsequent lumbar punctures revealed the same pattern of cerebrospinal fluid findings with the white blood cells varying from 57 to 150 per cubic millimeter. During the first forty-eight hours in the hospital several generalized convulsions occurred. Thereafter, the infant remained unconscious. During this period nuchal rigidity developed and generalized muscular twitchings were intermittantly noted. Temporary but recurrent episodes of cogwheel rigidity were demonstrated in all extremities. No abnormalities were detected in the deep tendon reflexes. The rectal tem-

From the Departments of Bacteriology and Pathology, Emory University School of Medicine and the Pediatric Service, Grady Memorial Hospital.

*Present address: Lawson Veterans Administration Hospital, Chamblee, Ga.

perature varied from 100° to 104° F. Treatment with penicillin, sulfadiazine, and streptomycin failed to influence the course of the disease. The patient died on the eighth hospital day and the twelfth day of clinical illness.

Pathologic Findings.—At autopsy, performed six hours after death, the pertinent findings were limited to the brain and lungs. The brain was moderately soft and weighed 1,160 grams. Flattening of the cortical convolutions was observed. The meningeal blood vessels were moderately congested. Extensive atelectasis was seen in the lungs.

Microscopic Examination: Sections of brain were fixed in formalin and stained with phloxine and with hematoxylin or methylene blue. The leptomeninges of the cerebral cortex were uniformly infiltrated with many mononuclear inflammatory cells. There was slight cellular infiltration in the leptomeninges of the cerebellum.

Examination of multiple sections of every lobe of both cerebral hemispheres revealed a uniform pathologic process that obscured the demarcation between gray and white matter in some areas. Numerous foci of spongy necrosis were observed in the cortex and underlying white matter. Almost all the ganglion cells were abnormal. Some were completely destroyed and their positions were represented by small cystic spaces. Others remained as fragments of cytoplasm or contained shrunken and pyknotic nuclei that had migrated to the edge of the cytoplasm. Glial cells, predominately astrocytes and oligodendroglia, were slightly increased in number. Many small petechial hemorrhages were observed. There were a few neuronophagic nodules and moderate perivascular accumulations of lymphocytes and macrophages in the right temporal cortex.

Areas of spongy necrosis and perivascular mononuclear cell infiltration were seen in sections of the thalamus and internal capsule. Ganglion-cell degeneration and perivascular infiltration were noted in the pons and in the midbrain at the level of the trochlear nerve nucleus. The only abnormalities seen in the medulla oblongata and the cervical spinal cord were rare focal perivascular infiltrations and neuronophagic nodules. No lesions were noted in the caudate nucleus, putamen, cerebellar folia, dentate nucleus, or the sacral spinal cord.

Type A intranuclear inclusion bodies were seen in all sections of the cerebral cortex, the subcortical white matter, and the thalamus. Most of the inclusions were amorphous or ill-defined particulate eosinophilic masses, but some were discrete rounded bodies. They were often surrounded by a pale-staining area or "halo" and the remnants of the nuclear chromatin were condensed at the periphery of the nucleus. The majority of the inclusion bodies were observed in oligodendroglia. Occasionally they were seen in astrocytes and ganglion cells.

There was a generalized infiltration in the interstitial tissue of the lungs by lymphocytes and macrophages. A few macrophages and a small amount of pink-staining amorphous material were seen in the lumina of the alveolar ducts and alveoli.

ISOLATION OF VIRUS FROM BRAIN

Sections of frontal, parietal, and occipital cerebral cortex, cerebellar cortex, pons, and cervical spinal cord were obtained with aseptic technique at post-mortem examination. A 20 per cent suspension of a pool of the brain sections was made in 10 per cent tryptose phosphate broth and centrifuged 1,500 r.p.m. for ten minutes. The supernatant fluid was injected intracerebrally in 0.03 c.c. amounts into 8-gram Swiss mice. The brains of two mice that showed signs of central nervous system irritability five days after inoculation

were removed, extracted, and injected as a 20 per cent suspension intracerebrally into a second group of mice. These mice developed signs of central nervous system irritability and died two to three days after inoculation. Thereafter, consecutive intracerebral passage of mouse brain material produced ruffled hair, hunched back, irritability, convulsions and death in mice from two to five days after inoculation depending on the concentration of the brain suspension employed. In all, forty intracerebral passages were made. The intracerebral LD_{50} titer in mice varied from $10^{-3.0}$ to $10^{-4.8}$. On two occasions a 20 per cent mouse brain suspension was passed through a porcelain filter (Selas 02), which retains bacteria and the larger viruses, without loss of infectivity for mice.

PATHOGENIC RANGE OF THE VIRUS AND PATHOLOGY IN INFECTED ANIMALS

Guinea pigs and rabbits inoculated intracerebrally with the virus developed signs of central nervous system disease and died five to six days after injection. The virus, inoculated on the chorioallantoic membrane of 14-day-old chick embryos, produced discrete white papular lesions. Histologic examination of the brains of infected mice and rabbits revealed large numbers of acidophilic intranuclear inclusion bodies.

IMMUNOLOGIC IDENTIFICATION OF THE VIRUS

Intracerebral neutralization tests, employing virus dilutions and undiluted sera, were performed as recommended by Olitsky and Casals[7] except that incubation was performed at 25° C. for one hour. Sera were heated at 56° C. for thirty minutes before use. Computation of the LD_{50} titer was performed by the method of Reed and Muench.[8] The neutralization index was calculated by determining the antilogarithm of the difference of the log LD_{50} of the virus with control serum and the log LD_{50} of the virus with immune serum.

Sera of proved neutralizing quality for Semliki Forest, western equine encephalitis, eastern equine encephalitis, and lymphocytic choriomeningitis viruses, employed in intracerebral neutralization tests, did not protect mice from the isolated virus (J virus). When virus of high infectivity and potent immune serum were employed it was possible to immunologically identify the J virus as a strain of

TABLE I. IDENTIFICATION OF J VIRUS AS A STRAIN OF HERPES SIMPLEX VIRUS. RESULTS OF INTRACEREBRAL MOUSE NEUTRALIZATION TESTS

SERA	VIRUS	VIRUS DILUTION						LD_{50}	NEUTRALIZATION INDEX
		10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}		
Normal domestic rabbit	J	–	4/4*	4/4	1/3	1/4		4.0	
Herpes simplex immune guinea pig (JRS-RT)†	J	2/4	1/4	0/3	1/4	–		1.4	400
Normal domestic rabbit	HF	5/5	5/5	5/5	4/5	0/5		4.4	
J immune guinea pig	HF	5/5	2/5	0/4	0/5	0/5		1.8	400
Normal domestic rabbit	J	–	5/5	5/5	3/5	3/5	0/5	4.8	
J immune guinea pig	J	5/5	2/5	1/5	0/5	0/5		2.0	630

*Numerator = mice that died; denominator = mice inoculated.
†Obtained from Dr. J. E. Smadel.

herpes simplex virus. As indicated in Table I herpes simplex immune serum protected mice against J virus and J immune serum protected mice against HF strain of herpes simplex virus and J virus.

Dr. Isaac Ruehman of Cincinnati, Ohio, has studied this virus. By cross resistance and neutralization tests he also demonstrated that J virus is a strain of herpes simplex.[9]

DISCUSSION

It has been established that herpes simplex virus occasionally causes fatal human encephalitis. Five fatal cases (including the one presented here) have been studied that satisfy the requirements for making the diagnosis: isolation of herpes simplex virus from brain tissue, histologic evidence of encephalitis, and demonstration of eosinophilic intranuclear inclusion bodies.

Further evidence of the etiological relationship of herpes simplex virus to certain cases of encephalitis can be provided by demonstrating that the encephalitis represents the primary infection. The absence of herpes simplex protective antibodies in the serum of a patient at the onset of encephalitis is an indication of primary infection because people once infected with herpes simplex virus ordinarily develop and maintain specific neutralizing antibodies for many years. No serological or clinical information is available to indicate whether or not the encephalitis in the four previously reported fatal cases was a manifestation of primary or of recurrent herpes simplex infection. It does seem reasonable, though, to suppose that the encephalitis that occurred in the 4-week-old infant[1] was part of the primary infection. In the patient reported here, definite information is available that the encephalitis occurred during an initial infection. Serum taken on the eighth day of disease contained no demonstrable neutralizing or complement-fixing antibodies for herpes simplex virus. Therefore, in this case and probably also in the 4-week-old infant the isolated virus cannot have represented latent virus from an earlier infection.

There is much to be learned about herpes simplex infections and particularly about infections of the central nervous system. By analogy to other virus diseases, many cases of "aseptic meningitis" caused by herpes simplex virus would be expected for each frank case of encephalitis. Although such infections are presumed to occur, at the present time they are not commonly recognized. Further information is also required to understand the pathogenesis of herpes simplex brain infection. As yet, symptomatic central nervous system infections with herpes simplex have not been proved to occur in the many persons who have recurrent herpes febrilis. It is possible that immune mechanisms prevent nervous symptom manifestations and that encephalitis is usually a manifestation of primary infection.

SUMMARY

A virus, identified as a strain of herpes simplex, was isolated from the brain of an infant who died during an illness characterized by signs of encephalitis. Acidophilic intranuclear inclusion bodies and encephalitic changes were seen in histologic sections of the brain. The absence

of herpes simplex neutralizing antibodies in the patient's serum on the eighth day of illness indicated that the encephalitis represented a primary infection with the virus.

REFERENCES

1. Smith, M. G., Lenette, E. H., and Reames, H. R.: Isolation of the Virus of Herpes Simplex and the Demonstration of Intranuclear Inclusions in a Case of Acute Encephalitis, Am. J. Path. **17**: 55, 1941.
2. Whitman, L., Wall, M. J., and Warren, J.: Herpes Simplex Encephalitis; a Report of Two Fatal Cases, J. A. M. A. **131**: 1408, 1946.
3. Zarafonetis, C. J. D., Smadel, J. E., Adams, J. W., and Haymaker, W.: Fatal Herpes Simplex Encephalitis in Man, Am. J. Path. **20**: 429, 1944.
4. Armstrong, C.: Herpes Simplex Virus Recovered From the Spinal Fluid of a Suspected Case of Lymphocytic Choriomeningitis, Pub. Health Rep. **58**: 16, 1943.
5. Fisher, J. W., and Patrick, J. W.: The Isolation of Herpes Simplex Virus From a Case of Polioencephalitis, Canad. M. J. **57**: 260, 1947.
6. Janbon, M., Chaptal, J., and Labraque-Bordenave, M.: Le Problème de La Méningite Herpétique; Contribution a son Étude Clinique et Expérimentale, Presse med. **50**: 145, 1942.
7. Olitsky, P. K., and Casals, J.: Neutralization Tests for Diagnosis of Human Viral Encephalitides, J. A. M. A. **134**: 1224, 1947.
8. Reed, L. J., and Muench, H.: A Simple Method of Estimating Fifty Percent Endpoints, Am. J. Hyg. **27**: 493, 1938.
9. Ruchman, I.: Personal communication.

INFECTIOUS MONONUCLEOSIS IN THE NEGRO

A Review of the Literature With a Report of Nine Cases

John F. Harley, M.D.
Louisville, Ky.

THIRTY-SEVEN years after infectious mononucleosis was recognized, the first case occurring in a Negro was reported in 1922 by Longcope.[1] After this one case, and in spite of the many articles on the various aspects of the disease, no more cases were reported in the Negro for another twenty-two years.

Bernstein,[2] in his noted study of the disease in 1940, reported the cases of sixty-five patients seen at Johns Hopkins Hospital, none of whom were Negroes. He stated that sporadic cases of infectious mononucleosis might be overlooked unless studied by repeated differential blood counts. Therefore, many of his patients were medical students and nurses who were admitted to the hospital for treatment of even minor illnesses. He explained that this may account for the paucity of cases observed in the dispensary and public wards, and for the fact that only one case had been reported in the Negro. Wintrobe[3] in 1942 noted that the disease in the Negro was limited to one case.

However, Werlin, Dolgopol, and Stern[4] at the Willard Parker Hospital in 1941 had included four cases in Negroes in a total of twenty-one cases reported. One case was reported in detail, and in this the heterophile antibody titer was positive 1:112. These were the first serologically proved cases in the Negro.

The next report in the Negro was by Johnson[5] in 1944. This was of two cases in children at the New Haven Hospital. Also in 1944 Ray and Cecil[6] reported three serologically proved cases in the Negro at the Medical College of Virginia Hospital, one of which was complicated by sickle-cell anemia.

In 1945 Blain and Vonder Heide[7] reviewed the literature and added six cases, making a total of sixteen cases reported in the Negro. These six cases represented 30 per cent of a series of twenty cases seen at Detroit Receiving Hospital during the previous ten years. Five of the cases were serologically confirmed. The authors concluded that infectious mononucleosis at that hospital was relatively as common in the Negro as in the white. They also felt that the widespread belief that infectious mononucleosis was rare in the Negro, was no longer tenable.

No further cases of infectious mononucleosis in the Negro were published until 1946, when Wechsler and Rosenblum[8] reported on an epidemic occurring at an Army post. In this epidemic, forty-nine Negroes, or 8.7 per cent of the total, suffered from the disease. The incidence in Negro patients was larger than their proportionate number on the post.

From the Department of Pediatrics, University of Louisville School of Medicine and the Louisville General Hospital.

TABLE I. DATA ON CASE HISTORIES

CASE	AGE	ADMITTING DIAGNOSIS	SYMPTOMS ON ADMISSION	REPRESENTATIVE W.B.C.	REPRESENTATIVE DIFFERENTIAL BLOOD COUNT	REPRESENTATIVE HETEROPHILE	HOSPITAL DAYS	FINAL DIAGNOSIS
1. M. G.	7 yr.	Possible Tbc. Possible leucemia	Generalized adenopathy, tonsillitis, fever	9,500	Polymorphonuclears 25 Eosinophiles 1 Lymphocytes 73	1:112	14	Infectious mononucleosis
2. J. T.	2 yr.	Possible diphtheria	Generalized adenopathy Membranous tonsillitis	8,600	Polymorphonuclears 57 Stab 5 Lymphocytes 38*	1:112	3	Infectious mononucleosis
3. J. T. (twin of above)	2 yr.	Possible diphtheria	Generalized adenopathy Membranous tonsillitis	8,800	Polymorphonuclears 65 Lymphocytes 35	1:224	3	Infectious mononucleosis
4. B. B.	9 mo.	Possible leucemia	Generalized adenopathy	6,100	Polymorphonuclears 34 Lymphocytes 64*	1:224	12	Infectious mononucleosis
5. A. M.	5 yr.	Measles Possible Tbc. adenopathy	Maculopapular rash Generalized adenopathy	7,100	Polymorphonuclears 58 Eosinophiles 15 Lymphocytes 24*	1:224	6	Infectious mononucleosis
6. N. S.	4 yr.	Possible diphtheria	Membranous tonsillitis	13,500	Polymorphonuclears 23 Lymphocytes 68	1:112	8	Infectious mononucleosis
7. L. D.	5 yr.	Possible diphtheria	Membranous tonsillitis	12,660	Polymorphonuclears 27 Eosinophiles 7 Lymphocytes 57* Monocytes 9	1:224	38	Infectious mononucleosis
8. R. Bc.	5½ yr.	Possible diphtheria	Generalized adenopathy Membranous tonsillitis	16,200	Polymorphonuclears 43 Lymphocytes 57*	1:224	6	Infectious mononucleosis
9. J. E.	5 yr.	Possible diphtheria	Generalized adenopathy Membranous tonsillitis	8,900	Polymorphonuclears 34 Lymphocytes 56* Monocytes 10	Negative	6	Infectious mononucleosis

*Typical mononuclear cells with irregular nucleous and foamy cytoplasm.

The next year Stewart[9] published what he believed to be the seventh case in the Negro. This, of course, was the sixty-sixth to be reported.

In 1948 Creaturo, Akerson, and Flanagan[10] reported twenty-four cases occurring at the New Haven Hospital, one of which was in a Negro girl. Also Saleiro, Brandao, and Torres[11] described the second case of infectious mononucleosis in the Negro to be published in Brazil. Another single case in the Negro was reported by Wilson, Ward, and Gray[12] in 1949. This case was complicated by hemolytic anemia, but the patient recovered after splenectomy.

CLINICAL STUDY

The occurrence of this disease in nine Negroes in a series of fifteen cases seen on the Pediatric Service of the Louisville General Hospital from 1946 through 1950 substantiates the opinion of Blain and Vonder Heide that infectious mononucleosis is relatively as common in the Negro as in the white. At his hospital, only diagnostic problems, or those patients who are very acutely ill, are admitted to the Pediatric Service because of lack of facilities. A far greater number of patients are treated on an out-patient basis through the clinics.

The cases to be presented represent 60 per cent of the total cases, and all were admitted from the clinics. The majority were admitted as diagnostic problems, usually to rule out the presence of diphtheria. Eight patients had heterophile agglutination titers of at least 1:112, while one patient was seronegative. He had, however, positive clinical and hematologic evidence for the diagnosis.

CASE REPORTS

The cases are presented in chart form as it is believed nothing would be added to the literature by presenting each history separately. Representative total and differential blood counts are given, as is the representative heterophile test in each case. Six of the cases were admitted to the hospital to rule out diphtheria. In each of these cases membranous tonsillitis was present, but repeated smears and cultures of the nasopharynx were negative for *Corynebacterium diphtheriae*. However, two patients were given diphtheria antitoxin before results of the cultures were obtained.

All of the cases presented were in the North American Negro. Ages varied from 9 months to 7 years. Hospital stay ranged from three to thirty-eight days, varying with the severity of the illness and also the difficulty in differential diagnosis. It is interesting to note that Case 3, J. T., was admitted to the hospital six months later with the same symptoms. At this second admission, *C. diphtheriae* were cultured from the throat and the child was treated for diphtheria with diphtheria antitoxin and penicillin with good results.

COMMENT

The nine cases of infectious mononucleosis in the Negro presented here represent 60 per cent of a series of fifteen patients who were admitted and diagnosed on the Pediatric Service at the Louisville General Hospital in the past five years. It is emphasized that these were diagnostic problems and probably many more were recognized and treated as out-patients.

During the past five years, 58,718 patients were seen in the Pediatric Clinic. There has been no tabulation as to the proportion of Negro to white patients treated, but from close observation over a period of months, the percentage of Negro children seen is about 50 per cent. In this period, 5,948 patients were admitted to the Pediatric Service, and of those admitted, 2,057, or 33 per cent, were Negroes.

CONCLUSION

Inasmuch as these cases were sporadic rather than epidemic, it is believed that the disease is as common in the Negro as in white at this hospital.

SUMMARY

1. Nine cases of infectious mononucleosis in Negroes are reported. Eight of these were serologically confirmed.

2. These cases bring the total of sporadic cases reported to twenty-nine. Including the epidemic of forty-nine cases in 1945 at Fort Bliss, Texas, the total of cases in the Negro reaches seventy-eight reported throughout the literature.

3. Infectious mononucleosis at this hospital is at least as common in Negro children as in white children.

4. The majority of these patients were admitted because of suspected diphtheria.

5. This series further substantiates the conclusions made in 1945, that infectious mononucleosis is relatively as common in the Negro as in the white.[7]

REFERENCES

1. Longcope, W. T.: Am. J. M. Sc. **164**: 781, 1922.
2. Bernstein, A.: Medicine **19**: 85, 1940.
3. Wintrobe, M. M.: Clinical Hematology, Philadelphia, 1942, Lea & Febiger.
4. Werlin, S. J., Dolgopol, V. B., and Stern, M. E.: Am. J. M. Sc. **201**: 474, 1941.
5. Johnson, R. D.: J. A. M. A. **124**: 1254, 1944.
6. Ray, E. S., and Cecil, R. C.: South M. J. **37**: 543, 1944.
7. Blain, A., and Vonder Heide, E. C.: Am. J. M. Sc. **209**: 587, 1945.
8. Wechsler, H. F., Rosenblum, A. H., and Sills, C. T.: Ann. Int. Med. **25**: 113, 1946.
9. Stewart, D. N.: U. S. Naval Med. Bull. **47**: 89, 1947.
10. Creaturo, N. E., Akerson, I. B., and Flanagan, M. M.: Connecticut M. J. **12**: 526, 1948.
11. Saleiro, J., Brandao, H., and Torres, M.: Hospital, Rio de Janeiro **33**: 409, 1948.
12. Wilson, S. J., Ward, C. E., and Gray, L. W.: Blood **4**: 189, 1949.

THE ELECTROCARDIOGRAM IN THE FIRST TWO MONTHS OF LIFE

ROBERT A. FURMAN, M.D., AND WILLIAM R. HALLORAN, M.D.
CLEVELAND, OHIO

INTERPRETATION of the electrocardiogram in infancy is complicated by the profound changes which accompany normal growth, changes whose pattern and normal variations are as yet inadequately documented. The earliest studies of the normal electrocardiogram in childhood employed only the three standard limb leads and a relatively small number of cases to cover the period from birth to adolescence. The first few months of infancy were dismissed with the observation that a "right preponderance" was found at this time.[1, 2] Subsequent reports of the normal three-lead electrocardiogram in childhood, although including adequate numbers of records, either omitted this period[3] or ignored it by considering the first six months as one homogeneous group.[4] The initial studies of the precordial electrocardiogram in childhood again dismissed this early period either by omitting it[5, 6, 7] or by considering the first year or so as one group.[8, 9, 10] Three recent studies of the unipolar electrocardiogram have well documented the appearance of the normal record in the first week of life,[11, 12, 13] but again the period of greatest normal variation and transition escaped practical analysis: in the first report by limiting the study to the first week of life; in the second by employing a method of unipolar lead determination not in common clinical usage; and in the third by placing all records from the eighth day to the fourth month in one group. Only in Ziegler's work has this period received the careful serial analysis necessary. His preliminary report[14] is, however, primarily a descriptive discussion limited to the precordial leads.

It is the purpose of this study to trace the normal electrocardiographic pattern of development during this period of so-called "right ventricular preponderance," the period of transition from the newborn toward the adult type of record; to do this by means of the twelve-lead electrocardiogram, followed serially in some patients; and to present this data in a manner which will facilitate more accurate clinical interpretation during this period.

METHOD OF STUDY

A series of seventy electrocardiograms were analyzed. These records were obtained from fifty-two patients, six of whom had from two to five serial tracings. Twenty patients were selected at random from the newborn nursery at MacDonald House, while the remaining thirty-two patients were selected from Babies and Children's Hospital. All of these latter patients had negative chest roentgenograms and either had been proved to have no disease or were concluding a long hospital stay following a minor illness, their hospitalization being prolonged

From the Department of Pediatrics and the Department of Medicine, Western Reserve University School of Medicine and Babies and Children's Hospital.

for other than medical reasons. The patients were all submitted to examination by one of us in addition to the routine examination by the intern and assistant resident. Patients with soft systolic murmurs were not excluded.

All the records were taken on a Cambridge "All Electric Mobile Electrocardiograph and Stethograph." All patients were supine and were offered Karo water if necessary. Standard Cambridge infant extremity electrodes and a special 2.0 cm. precordial electrode were employed. Care was taken to wipe the chest clean of electrode jelly after each precordial lead. Twelve leads were obtained on each patient: the three standard leads, the augmented unipolar limb leads, and the six standard precordial V leads. In a small number of patients additional precordial leads were obtained, either from the right side of the precordium corresponding to V_4 and V_6 or from V_7 and V_8 on the left side.

Two important departures from standard procedure must be noted: first, the paper speed was accelerated to 50 mm. per second; second, all precordial leads were taken with the string "half-standardized," so that one millivolt produced a deflection of the string of only 5 mm. The first of these steps was taken to enable us to make accurate time measurements despite the rapid rates in this age group. The second was taken because of the high voltage of some of the precordial QRS complexes to insure against any deflection being out of the range of the paper. Both these departures have proved most satisfactory from a practical standpoint and have been adopted as routine for all pediatric electrocardiograms. The second of these changes may, however, be unfortunate for a study of this type as minor errors of 1.0 mm. or less in standardization were quite common and were capable of producing significant errors of up to 16 per cent when the deflection measurements were doubled for comparison with records obtained with the conventional standardization. Correction was made for any standardization error of greater than 1 mm. The smallest unit of measurement employed for amplitude of waves was 0.5 mm.

The records were obtained so that there were twenty taken in the first week of life and ten each in the second, third, and fourth, and in the fifth through sixth, and seventh through the eighth weeks. All data were analyzed initially on the basis of these six groups to determine the effect of age on each of the measurements made.

RESULTS

1. *Mechanism.*—Normal sinus rhythm was present in all the records, with twelve showing a mild sinus arrhythmia. There was a wandering pacemaker in one of the records having sinus arrhythmia. Occasional premature ventricular beats were noted in one record, occasional premature auricular beats in another. One of the patients with sinus arrhythmia had five serial records, the arrhythmia being present in just two of these records. Tudbury and Atkinson[13] noted a slightly higher incidence of sinus arrhythmia which might easily be explained by the fact that with a normal paper speed their leads contained twice as many complexes and their opportunity for detecting minor arrhythmias was consequently greater.

2. *Heart Rate.*—In the entire group the rates varied from 102 to 182 per

minute. Slower rates tended to occur in the younger groups, no rate below 130 being found after the third week; the average rates for the groups in the first three weeks varying between 136 and 144, in the fourth through eighth weeks between 150 and 157. Our means of 140 for the first week and 155 for the subsequent weeks compare closely with those of Tudbury and Atkinson[13] of 148 and 163, respectively.

5. *Duration of Electrical Systole.*—In measuring the duration of electrical systole or Q-T interval only the six limb leads were used. The Q-T duration that was selected was the longest one that could be found in two or more leads, the final determination being the average of three measurements in the lead selected. The rate selected for the record was the rate in this lead. K was calculated for all records according to the formula of Bazet ($K = QT \sqrt{RR}$). K was found to vary between 0.332 and 0.447 on a normal distribution curve as shown in Table I, with a mean of 0.388 and a standard deviation of 0.022. Statistically there was no significant difference between the different age groups. These values are surprisingly similar to those of

TABLE I. DISTRIBUTION TABLE FOR BAZET'S CONSTANT OF ELECTRICAL SYSTOLE

K	AGE IN WEEKS						TOTAL
	1ST	2ND	3RD	4TH	5-6TH	7-8TH	
0.30-0.3199							
0.32-0.3399	2						2
0.34-0.3599	3	2	1	1		1	8
0.36-0.3799	3	1	1	2	2	1	10
0.38-0.3999	6	3	5	5	8	5	32
0.40-0.4199	3	4	2	2		2	13
0.42-0.4399	2		1			1	4
0.44-0.4599	1						1
0.46-0.4799							

TABLE II. PERCENTAGE DISTRIBUTION OF ELECTRICAL POSITION

WEEK	VERTICAL TO RIGHT (PER CENT)	VERTICAL (PER CENT)	SEMIVERTICAL (PER CENT)	INTERMEDIATE (PER CENT)
1st	55	45	--	--
2nd	50	50	--	--
3rd	20	70	10	--
4th	--	50	40	10
5th-6th	--	60	20	20
7th-8th	--	20	50	30

3. *P-R Interval.*—The P-R intervals varied between 0.08 and 0.13 sec. with 91 per cent between 0.09 and 0.12, the average being 0.103. This last figure checks well with that of Tudbury and Atkinson[13] who obtained a mean of 0.10. There was no demonstrable variation with either age or rate.

4. *QRS Duration.*—The duration of the QRS complexes varied between 0.04 and 0.07 with 93 per cent measuring either 0.05 or 0.06, the average being 0.054. No correlation with heart rate was observed, but it was noted that the duration tended to be shorter in the first four weeks. In this group 72 per cent were 0.05 or less, while in the last four weeks only 20 per cent were 0.05 or less. Again these observations check closely with those of Tudbury and Atkinson.[13]

Alimurung and associates[15] who found a mean K of 0.386 with a standard deviation of 0.019 for twenty-six patients in the first month of life.

6. *Electrical Position.*—In determining the electrical position in the age group under study, it was found is readily apparent that the designation "vertical to the right" is somewhat a misnomer, as records in this group could perhaps be more accurately called semivertical to the right and intermediate to the right, respectively. Subdivision of the records in

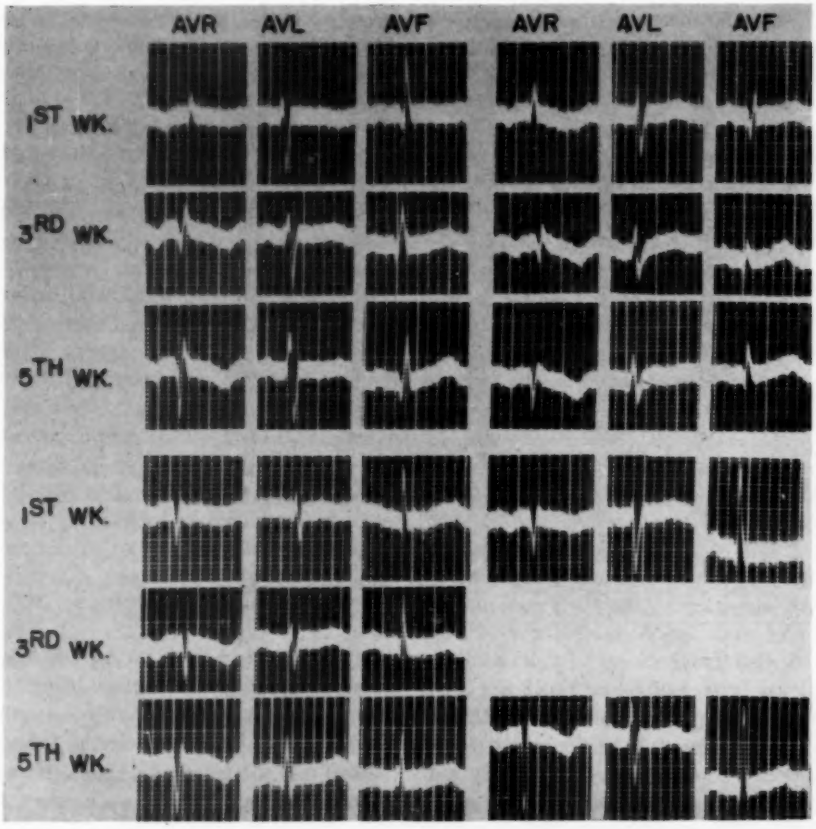


Fig. 1.—Changes in electrical position accompanying normal growth as revealed by serial augmented unipolar extremity leads in four patients.

advantageous to use the term "vertical to the right" to describe those records with a negative deflection in aV_L and a positive deflection in aV_F, and in which the R wave in aV_R was greater than the negative deflection. It the "vertical to the right" group on this basis did not seem justifiable because of the small number of records in the group. Table II reveals that whereas this was the position in over one-half in the first two weeks, it was

not noted from the fourth week on. This table also reveals that while about half the records in the fourth through eighth weeks had a semivertical or intermediate position, only one of forty records in the first three weeks had such an electrical position. This latter finding is confirmed by Schaffer and collaborators[12] who found aV_L to be a negative deflection in their fifty newborn infants. Tudbury and Atkinson's[13] finding of five newborn infants out of forty-six with semivertical, semihorizontal, or horizontal hearts is at slight variance with these observations.

Fig. 1 illustrates these progressive changes in electrical position in four patients who were followed with serial records, the two on the top row having hearts in the "vertical to the right" position as newborn infants, the two on the lower row having vertical hearts as newborn infants. It is interesting to observe that of the six patients followed with serial records three initially had vertical to the right hearts, while three had vertical hearts. By the age of six weeks there was one vertical, one semivertical, and one intermediate heart in each of these two groups.

7. *Axis Deviation.*—Table III shows that 50 per cent of the records in the first three weeks had axes greater than 105 degrees whereas only 10 per cent had axes in excess of 105 degrees from the fourth week on. It is pertinent to note that in each group there were about 30 per cent with axes between 90 and 105 degrees. In the first three weeks no axis was less than 73 degrees, whereas the lower limit in the last five weeks was 11 degrees. These figures are difficult to compare with those of Tudbury and Atkinson[13] except that for the first week our mean of 108 degrees is identical with theirs as is our percentage of normal axes and right axis deviations. Table III thus reflects the diminution in right ventricular preponderance after the third week as determined above by inspection of the unipolar limb leads although the cleavage is not quite so sharp. From the fourth week through the eighth week the 63 per cent normal axes and the mean axis of 74 degrees are both similar to the data for the above authors' Group II, which covered the second week through the fourth month.

TABLE III. PERCENTAGE DISTRIBUTION FOR AXIS DEVIATION

WEEK	ABOVE 120° (PER CENT)	105-120° (PER CENT)	90-105° (PER CENT)	BELOW 90° (PER CENT)
1st	35	25	30	10
2nd	10	50	30	10
3rd	--	30	40	30
4th	10	10	20	60
5th-6th	--	10	30	60
7th-8th	--	--	30	70

8. *P Wave.*—Table IV lists the range and mean amplitude of the P waves for the entire group. There were no significant differences between the smaller subgroups. The duration of the P waves varied from 0.02 to 0.08 with 97.5 per cent measuring 0.06 or less. In no record did more than two leads have P waves of duration greater than 0.06 and in only six records were there two leads of this duration. Inverted P waves were found four times

TABLE IV. SUMMARY OF P-, Q-, AND T-WAVE AMPLITUDES, EXPRESSED IN MILLIMETERS, RANGE BEING LISTED ABOVE MEAN.* HALF STANDARDIZATION EMPLOYED FOR PRECORDIAL LEADS

WAVE DATA	I	II	III	aV_R	aV_L	aV_F	V_1	V_2	V_3	V_4	V_5	V_6
P range	0.5-2.0	1.0-3.0	−1.0-2.0	−1.0- −2.0	−1.0-1.0	0.5-2.0	−1.0-1.5	0.5-2.0	0.5-2.0	0.5-1.5	0.5-1.5	0.5-1.5
mean	1.1	1.9	1.1	−1.3	0.6	1.1	0.7	0.7	0.7	0.7	0.6	0.6
Q range	0.5-2.0	0.5-6.0	0.5-6.0	0.5-13.0	0.5-5.0	0.5-6.0	--	--	0.5-1.0	0.5-4.0	0.5-2.0	0.5-2.0
mean	65% Abs.	1.2	2.2	60% Abs.	80% Abs.	1.6	100% Abs.	100% Abs.	97% Abs.	84% Abs.	56% Abs.	35% Abs.
T 1st and 2nd	0-2.5	−0.5-4.0	−1.5-3.0	0- −3.0	−0.5-2.0	1.0-3.0	−3.5-3.0	−3.0-3.0	−4.0-2.0	−3.0-3.0	0-3.0	0-3.0
weeks	1.3	1.5	--	−1.5	--	--	--	--	--	--	0.7	0.7
T 3rd to 8th	1.5-3.5	1.0-5.0	−1.0-2.0	−1.0- −5.0	0-2.5	0.5-3.0	−3.0-0.5	−3.0-1.5	−2.0-3.0	−2.5-4.0	−1.0-4.0	0-3.0
weeks	2.2	2.8	--	−2.6	1.0	1.7	--	--	--	--	1.4	1.5

*The mean is not listed unless the wave was present and not inverted in more than 80 per cent of the group.
Abs. indicates deflection was absent.

in III, three times in aV_L and eleven times in V_1. Diphasic P waves were found four times in III, two times in aV_L, five times in V_1, six times in V_2, and twice in V_3.

The range noted for the P waves is quite similar to that listed by both Tudbury and Atkinson[13] and Schaffer and associates.[12] The latter noted that the P wave in $V_{sternum}$ was always upright, which we confirm by not noting any inversion in V_2 through V_6, although Tudbury noted occasional inversion as far out as V_4. The mean amplitude of P in the limb leads in our observations is almost double that found by Tudbury and Atkinson, while the means for the precordial leads, without correction for "half-standardization," are about equal. This is probably due to two facts already noted: first, our reluctance to attempt measurements less than 0.5 mm.; and second, the difficulty of accurate standardization using the method we employed.

9. *Q Wave.*—The range and amplitude of the Q waves are listed in Table IV. The only significant changes with age were an increase in the mean depth of Q in aV_R in the last five weeks from 7.5 to 13.0 and a sharp increase in the Q wave incidence in V_4 through V_6 after the first week. A Q wave was present in II in 80 per cent, in III in 81 per cent, and in aV_F in 87 per cent. These figures are quite similar to those of Tudbury and Atkinson.[13]

10. *S-T Junction.*—The nature of the S-T segment in many records in this group as it blends smoothly into the T wave precluded accurate measurement of the duration of this segment. The incidence of elevation or depression of the S-T junction from the isoelectric line of greater than 0.5 mm. was quite high. The incidence and degree of this deviation did not vary among the age groups. In Leads I and II elevation up to 1.0 mm. was present in 57 per cent, with depression of 0.5 mm. noted twice in II. Lead III was remarkable in that deviations were present in only 8 per cent and when present were not greater than 0.5 mm. Deviations up to 1.0 mm. were present in approximately 30 per cent of the unipolar limb leads and 40 per cent of the precordial leads. Depression of the junction up to 2.0 mm. was noted occasionally in the first week in V_2 and V_3. These observations are similar to those of the other observers.

11. *T Wave.*—The range and mean of the T-wave amplitudes are listed in Table IV. Although the range was approximately the same for the entire group, the mean took a rather sharp increase after the first two weeks so that the statistics are listed for two groups. T-wave inversion was always present in aV_R, never present in I or V_6, not seen after the first week in II or aV_L, and not seen after the second week in aV_F. Across the precordium, after the first week, T was inverted in 60 per cent in V_1, 40 per cent in V_2, 30 per cent in V_3, 5 per cent in V_4, and 2 per cent in V_5. In the first week 50 per cent showed no precordial T-wave inversion, diphasic T waves not being considered as inverted unless the negative phase was of greater amplitude than the positive. In two records in the first week of life the precordial T wave changed from positive or isoelectric to inverted and back again to positive or isoelectric, proceeding from right to left across the precordium. This was not noted after the first week. An inverted T wave in the presence of a large R wave or an upright T wave

TABLE V. SUMMARY OF R- AND S-WAVE MEASUREMENTS, RANGE BEING LISTED ABOVE THE MEAN. MEASUREMENTS ARE IN MILLIMETERS. HALF STANDARDIZATION EMPLOYED FOR PRECORDIAL LEADS.

	I	II	III	aV_R	aV_L	aV_F	V_1	V_2	V_3	V_4	V_5	V_6
R First two weeks	0.0-7.0	0.5-15.0	5.0-18.0	0-6.0	0-6.0	1.0-17.0	3.0-16.0	5.0-20.0	3.0-20.0	3.5-18.0	0.5-14.0	0-10.0
	2.0	7.6	11.0	3.3	3.3	8.3	7.1	10.8	10.5	9.1	6.1	4.7
R Third week	0.5-9.0	4.0-12.0	2.0-14.0	0-6.0	0-4.0	3.0-13.0	3.0-15.0	4.0-17.0	6.0-12.0	6.0-14.0	4.0-9.0	2.5-8.0
	3.6	7.0	8.3	2.0	2.3	6.9	7.2	10.4	9.0	9.8	6.2	4.9
R Fourth week	0.5-10.0	5.0-17.0	5.0-14.0	0.5-3.0	0-5.0	4.0-16.0	1.5-11.0	4.0-18.0	5.5-17.0	6.0-17.0	5.0-16.0	2.0-13.0
	6.1	10.4	8.5	2.1	2.3	8.1	7.0	12.8	12.1	11.5	11.1	7.8
R Fifth-eighth weeks	3.0-13.0	5.0-24.0	1.5-17.0	1.0-5.0	1.0-11.0	2.0-16.0	3.0-12.5	5.5-19.0	5.5-18.0	5.5-20.0	5.0-22.0	4.5-16.0
	8.1	12.8	9.7	2.9	5.1	9.3	6.0	12.7	12.4	13.8	11.5	9.0
S First two weeks	0-13.0	0-8.0	0-4.0	0-7.0	0-13.0	0-4.0	0-14.0	5.0-20.0	5.0-23.0	3.5-22.0	1.0-16.0	0-12.0
	6.2	2.2	0.7	2.1	7.2	0.8	4.8	11.3	11.8	11.4	7.6	5.3
S Third week	0-8.0	0-7.0	0-4.0	0-7.0	0-10.0	0-6.0	0-13.0	5.0-16.0	4.0-18.0	4.0-9.0	1.0-7.0	1.0-3.0
	3.6	1.1	0.4	3.2	4.6	0.8	5.2	8.8	8.1	6.8	4.0	2.1
S Fourth week	1.0-8.0	0-3.0	0.5-4.0	0-9.0	3.0-8.0	0-1.0	0-11.0	3.0-18.0	3.5-14.0	2.0-16.0	2.0-10.0	0-5.0
	5.0	1.4	0.6	3.7	5.5	0.4	4.9	10.2	8.8	6.6	4.5	2.5
S Fifth-eighth weeks	0-11.0	0-5.0	0-4.0	0-15.0	3.0-11.0	0-2.5	0-8.0	2.5-15.0	2.5-16.0	2.5-17.0	1.5-14.0	1.0-14.0
	5.3	2.0	0.7	4.4	6.2	0.6	2.9	8.7	9.0	9.2	6.9	3.8

in the presence of a large Q or S wave was noted not infrequently in all leads in the first week of life and frequently throughout the entire series in III, aV_L and V_1. It was not noted after the first week in II and V_6, after the second week in aV_R, aV_F, and V_2 through V_5. Schaffer and co-workers[12] noted this T-wave variability in their newborn group. It was in our series, as they noted, usually gone by the third day but did persist through the sixth day in one record. Our absolute values again compared well with Tudbury and Atkinson.[13] These changes were noted and very well documented by Ziegler.[14] We cannot confirm all of his observations in the first three days as we made no attempt to take serial records within this period.

12. *R and S waves.*—Table V lists the range and mean values for the R and S waves, the differences between the first and second weeks and the fifth-sixth and seventh-eighth weeks groups being small enough to warrant combining these respective groups. Tables II and III point out the important relationships for the R and S waves of the limb leads. These values

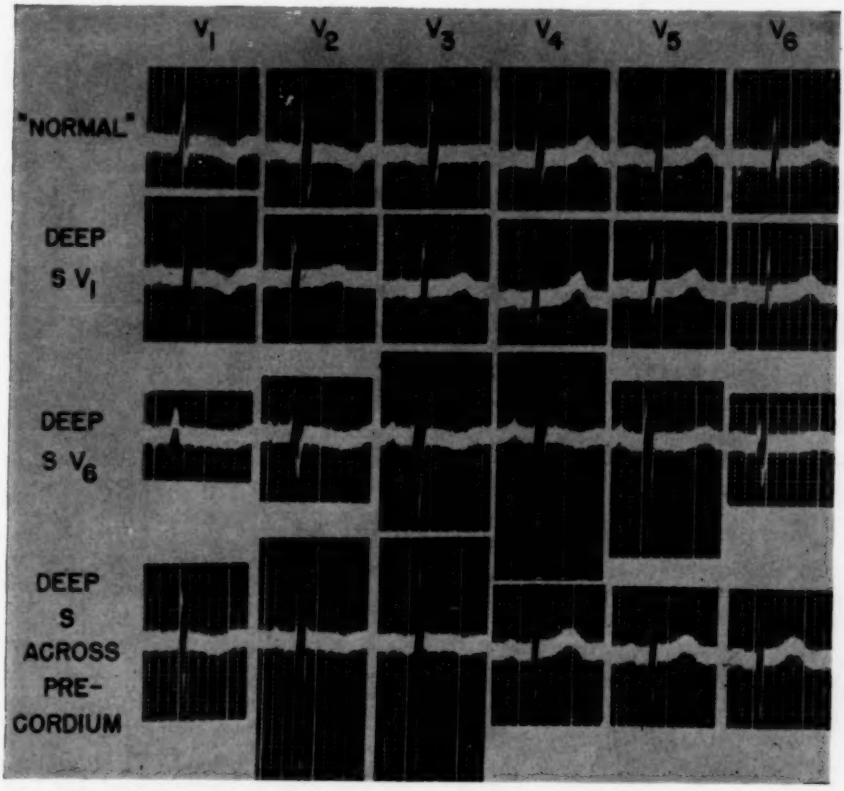


Fig. 2.—Precordial electrocardiographic patterns seen in the first two months of life. For details see text.

are difficult to compare with those of Tudbury and Atkinson[13] because of their different age groups. The general range of values for the limb leads, however, is similar, while those for the precordial leads are about equal although our figures are uncorrected for our method of precordial standardization. Our observations for the precordial leads are difficult to compare with those of Ziegler[14] as we did not determine the time of onset of the initial deflection and did not express the amplitude of the intrinsic deflection as a percentage of RS in the same lead.

"deep S in V_1" pattern being similar to the first except for the S in V_1 being equal to or greater than the accompanying R wave; (3) the "deep S in V_6" pattern being similar to the first except for the S in V_6 being equal to or greater than the accompanying R wave; (4) the fourth pattern having S waves across the entire precordium equal to or greater than the respective R waves. In those records with a deep S in V_1, a lead to the right in the midclavicular line usually revealed a tall R small S inverted T pattern. This was usually not the case with those having the "RS across the precordium" pattern. When a deep S was present in V_6 it was present also in V_7 or V_8 when those leads were obtained.

TABLE VI. PERCENTAGE DISTRIBUTION OF PRECORDIAL QRS PATTERNS

WEEK	DEEP S ACROSS PRECORDIUM (PER CENT)	DEEP S V_6 (PER CENT)	DEEP S V_1 (PER CENT)	"NORMAL" (PER CENT)
1st	45	45	5	5
2nd	10	30	10	50
3rd	--	--	40	60
4th	--	--	20	80
5th-6th	--	10	--	90
7th-8th	--	--	10	90

In evaluating the precordial R- and S-wave relationships, four rather distinct patterns of complexes were observed which are illustrated in Fig. 2: (1) the "normal" pattern having the R waves in V_1 and V_6 greater than the respective S waves, an inverted T usually being present in V_1, an upright T and a Q wave usually being present in V_6. The term "normal" was used to describe this pattern not because it is in any way similar to an adult type pattern, but rather because observation of a large number of tracings of normal infants has shown this to be the dominant pattern until around eighteen months. These latter records were taken as part of a study on the normal electrocardiogram in infancy and childhood which has not been completed at this date; (2) the

That there is justification for these arbitrary designations can be seen in Table VI in which the age distribution for each of these respective patterns has been tabulated. From this it can be seen that in the first week the precordial S pattern and the S-V_6 pattern predominate with but one "normal" pattern present. In the second week both of the former patterns are still present but much less frequently, with a few S-V_1 patterns and one-half of the tracings falling in the "normal" group. In the ensuing weeks the precordial S pattern and the S-V_6 pattern all but disappear with the S-V_1 pattern gradually diminishing in fre-

quency after reaching a peak in the third week and with the "normal" becoming the usual pattern.

DISCUSSION

From the foregoing it is obvious that certain electrocardiographic characteristics are quite constant during this period of the first two months: mechanism, heart rate, P-R interval, QRS duration, duration of electrical systole, S-T junction, P and Q waves. This, however, is not the case with the T waves, the electrical position, and the character of the precordial QRS complexes.

The T waves of the newborn infant were characteristically of low voltage and apparently independent of the character of the QRS complex as evidenced by: (1) frequent T wave inversion in aV_L, aV_F, and II; (2) absence of precordial T-wave inversion in one-half the records; (3) appearance of isolated precordial T-wave inversion over the left precordium; (4) presence in many leads of an inverted T wave with a large R wave or an upright T with a large Q or S wave. These characteristics were most frequent in the first two days of life, but were found as late as the sixth day. In the second week the voltage still tended to be low, but the T wave was assuming a more mature character with the apparent independence of the T wave noted above being found only in aV_R and V_2 through V_5. After the end of the second week these latter changes were no longer noted, the voltage increased, and the character of the T wave then remained constant through the remainder of the period under study.

It appears from our studies that in the first few days of life, probably even through the first week, little significance can be attached to T waves whose character by the usual standards would be considered abnormal. In the second week certain T-wave configurations, such as an inverted precordial T wave to the left of an upright or isoelectric T wave, can probably be called abnormal. It is not, however, until after the second week that the T waves can be judged by the usual standards.

Analysis of both axis deviation and electrical position indicates a definite reduction during the third week of the so-called right ventricular preponderance. As axes of greater than 90 degrees still persist after the third week in 30 per cent and as axes of greater than 105 degrees are occasionally found in this period, the practical value of this observation can be obscured if the axis deviation alone is considered. However, when the augmented unipolar leads are observed, it becomes clear that after the third week electrical axes greater than 90 degrees are due primarily to a negative deflection in aV_L of greater magnitude than the negative deflection in aV_R, rather than being due to the magnitude of the positive deflection in aV_R as was the case in the first three weeks. This observation has proved most helpful in the interpretation of records having axes greater than 90 degrees after the third week of life: this finding being a normal one if the positive deflection in aV_R is less than the negative deflection; the record probably being abnormal if the reverse is true.

The augmented unipolar leads are again helpful when it is realized that although axes as low as 73 degrees were noted in the first three weeks and as low as 11 degrees in the third through eighth weeks, there were no hearts in an intermediate or horizontal

position in the first three weeks, with only one semivertical heart in this group; and that in the fourth through eighth weeks there were no horizontal or semihorizontal hearts. Without measurement of the axis deviation, it has been most helpful just by inspection to be able to consider an intermediate or horizontal heart in the first three weeks and a semihorizontal or horizontal heart in the fourth through eighth weeks as probably abnormal.

Familiarity with the range of the normal electrical position in the first two months probably obviates the necessity of the V_{6R} and V_{4R} leads suggested by Schaffer[12] although they may be helpful in doubtful cases. Certainly in the first two cases of right ventricular hypertrophy he later reported,[16] the special right precordial leads yielded no information that was not available in aV_R. Both his patients with left ventricular hypertrophy were under one month of age and had horizontal hearts—an abnormal finding suggestive of left ventricular preponderance regardless of, although nicely confirmed by, the special right precordial leads.

The precordial QRS complexes in the first two weeks of life can normally assume so many different forms that they are of limited value in interpretation. There are, however, two constant characteristics: first, the R wave in V_1 should be equal to or greater than the S wave; second, a biphasic complex with positive and negative deflections of approximately equal magnitude should be present in either V_2, V_3, or V_4. The normal adult pattern is not seen normally in this age group and its presence would be indicative of left ventricular enlargement. Knowledge of this fact would have kept Knoop and Grishman[17] from calling normal, with no evidence of left ventricular hypertrophy, a record in a 2-week-old infant that they described as showing gradual progression from a small r deep S pattern over V_1 to the small q tall R small s pattern over V_6.

After the second week of life the appearance of a precordial pattern characterized by a deep S across the precordium is probably abnormal. The appearance of a deep S in V_6 after two weeks is likewise probably abnormal and can be suggestive of right ventricular hypertrophy. After the fourth week of life the appearance of a deep S in V_1 is unusual and should be checked by a precordial lead to the right of V_1.

The pattern characterized by the deep S across the precordium seen in the first two weeks is perhaps the result of the relatively large size of the heart compared to the chest wall, the leads being taken from a relatively small area overlying both ventricles. It is interesting to note that 83 per cent of those with a deep S in V_6 in the first three weeks were in a "vertical to the right" position, 86 per cent of those with a deep S in V_1 in the first three weeks were in a vertical position, while those with the deep S across the precordium and the "normal" patterns had the same electrical position distribution as did the entire group.

The above discussion is not meant to imply that this relatively small series establishes normal values for this age period. Rather, the developmental patterns and statistics are presented to form the tentative basis for the rational interpretation of records in this age group, standards to be confirmed by further clinical experience.

SUMMARY

A series of seventy electrocardiograms employing twelve leads were taken on fifty-two normal infants in the first two months of life. Analysis of these records revealed that:

1. The mechanism, heart rate, P-R interval, QRS duration, duration of electrical systole, S-T junction, P and Q waves are essentially constant during this period.

2. The T wave has unique characteristics in the first few days of life, but conforms to the hitherto accepted standards of behavior after the end of the second week, the second week being a type of transition period.

3. The relative right ventricular predominance characteristic of the first two months undergoes marked diminution during the third week of life, a change most easily demonstrated by the augmented unipolar extremity leads.

4. The precordial complexes have four characteristic patterns, the appearance of which follows a definite developmental course.

The data are presented and discussed in such a manner as to facilitate interpretation of electrocardiograms in the first two months of life.

The authors are indebted to Drs. Harold Feil and Charles F. McKhann for their stimulating encouragement and advice; to Dr. George Badger and Mr. Arthur Boblett of the Department of Preventive Medicine for the statistical interpretation of the data concerning the duration of electrical systole; to Mr. David Shields whose skill and patience made over one-half of our records possible; and to Dr. Harris D. Riley for assistance in taking the records on the newborn group.

REFERENCES

1. Krumbhaar, E. B., and Jenks, H. H.: Electrocardiographic Studies in Normal Infants and Children, Heart **6**: 189, 1917.
2. Seham, M.: The Electrocardiogram in Normal Children, Am. J. Dis. Child. **21**: 247, 1921.
3. Maroney, M., and Rantz, L. A.: Electrocardiogram in 697 Healthy Infants and Children, Pediatrics **5**: 396, 1950.
4. Burnett, C. T., and Taylor, E. L.: Electrocardiograms on 167 Average Healthy Infants and Children, Am. Heart J. **11**: 185, 1936.
5. Master, A. M., Dack, S., and Jaffee, H. L.: The Precordial Lead of the Electrocardiogram of Normal Children, Am. J. Dis. Child. **53**: 1000, 1937.
6. Goldberger, E.: Significance of Downward T Waves in Precordial Leads of Normal Children, Am. J. Dis. Child **71**: 618, 1946.
7. Suarez, R. M., and Suarez, R. M.: The T Wave of the Precordial Electrocardiogram at Different Age Levels, Am. Heart J. **32**: 480, 1946.
8. Battro, A., and Mendy, J. C.: Precordial Leads in Children, Arch. Int. Med. **78**: 31, 1946.
9. Switzer, J. L., and Besoain, M.: Electrocardiograms of Normal Children, With Special Reference to the aV Limb Leads and Chest Leads, Am. J. Dis. Child. **79**: 449, 1950.
10. Yu, P. N. G., Joos, H. A., and Katsampes, C. P.: Unipolar Electrocardiogram in Normal Infants and Children, Am. Heart J. **41**: 91, 1951.
11. Groedel, F. M., and Miller, M.: Electrocardiographic Studies in the Newborn, Exper. Med. & Surg. **2**: 110, 1944.
12. Schaffer, A. I., Burnstein, J., Mascia, A. V., Barenberg, P. L., and Stillman, N.: The Unipolar Electrocardiogram of the Newborn Infant, Am. Heart J. **39**: 588, 1950.
13. Tudbury, P. B., and Atkinson, D. W.: The Electrocardiograms of One Hundred Normal Infants and Young Children, J. PEDIAT. **36**: 466, 1950.
14. Ziegler, R. F.: Characteristics of the Unipolar Precordial Electrocardiogram in Normal Infants, Circulation **3**: 438, 1951.
15. Alimurung, M. M., Joseph, L. G., Craige, E., and Massell, B. F.: The Q-T Interval in Normal Infants and Children, Circulation **1**: 1329, 1950.
16. Schaffer, A. I.: Unipolar Electrocardiographic Studies in Congenital Heart Disease in Infancy, Am. J. Dis. Child. **80**: 260, 1950.
17. Kroop, I. G., and Grishman, A.: The Variability of the Electrocardiogram in Congenital Tricuspid Atresia, J. PEDIAT. **37**: 231, 1950.

USE OF ASCORBIC ACID TABLETS TO ENRICH MILK FOR INFANT FEEDING

ARTHUR D. HOLMES, PH.D.,* AND CARLETON P. JONES, B.S.,* AMHERST, MASS., AND FRANCIS TRIPP, M.S.,** NEW BEDFORD, MASS.

INFANTS, particularly during early life, subsist on a very restricted diet which ordinarily consists largely if not wholly of human or modified cow's milk. Milk has been frequently described as nature's most perfect food, but it is inadequate in such constituents as iron and reduced ascorbic acid (vitamin C). The deficiency in reduced ascorbic acid is usually compensated for by feeding orange juice to infants. Orange juice is an excellent fruit juice that is particularly acceptable to adults as well as children. In addition, orange juice is an important source of ascorbic acid; Lorenz[1] estimated that oranges contribute annually about 624,080,000 Gm. to the human dietary. Daniel, Kennedy, and Munsell[2] reported from 45 to 51 mg. of vitamin C per 100 c.c. of orange juice. In a study of the cost of vitamin C from fresh fruit juices, Holmes, Pigott, and Tripp[3] found from 32 to 64 mg. per 100 c.c. of orange juice. Subsequently, Holmes, Patch, and Tripp[4] reported values of from 27 to 67 mg. of ascorbic acid per 100 c.c. of juice, and they further indicated the variability of the ascorbic acid content of orange juice by noting that forty-four samples of juice gave twenty-six different values. Beacham and Bonney[5] reported that the vitamin C content of Florida oranges varies with picking date, geographical location, variety, and rootstock differences, and Harding, Winston, and Fisher[6] found higher vitamin C values for oranges picked from outside branches of the tree and well exposed to sunlight than for oranges picked from the interior of the tree. French and Abbott[7] concluded from their extensive investigation of oranges that there was no correlation between the concentration of reduced ascorbic acid in Florida oranges and their weight, amount of peel, or the volume of juice that they contained. This conclusion is in accord with that of Holmes, Patch, and Tripp,[4] who determined the relation of season, weight, and price to the vitamin C content of oranges, and stated the average purchaser cannot use the size or cost of oranges as a reliable guide to the amount of juice or of ascorbic acid which they may contain. These observations concerning the lack of uniformity in the amount of ascorbic acid in orange juice raised a question regarding the feasibility of correcting the ascorbic acid deficiency of milk used for infant feeding by adding the pure crystalline vitamin in tablet form to milk as it is fed to the infant, and this study was conducted to answer that question.

Contribution No. 784, Massachusetts Agricultural Experiment Station.

*From the Massachusetts Agricultural Experiment Station.

**From New Bedford Textile Institute.

EXPERIMENTAL

To test the permanency of ascorbic acid in enriched milk, a supply of

pasteurized milk was obtained from the Dairy Industry Department of the University at fourteen intervals between September of one year and August of the next year—an interval of eleven months. Synthetic ascorbic acid was dissolved in the pasteurized milk (75 mg. per liter), and this enriched milk was assayed at once for reduced ascorbic acid by the Sharp method[8] as modified by Holmes.[9] The samples were stored in a household-type refrigerator in darkness at 10° C. for ninety-six hours, and during this time additional assays were made at twenty-four-hour intervals. Since the fourteen samples of enriched milk were prepared at intervals during an eleven-month period, it was felt that they were representative of ascorbic acid-enriched pasteurized milk.

Ascorbic acid tablets for enriching milk for infant feeding may be prepared by compounding synthetic ascorbic acid with suitable materials for use as excipient or filler, disintegrator, binder, and lubricant. Lactose, or milk sugar, a normal constituent of milk, is frequently and satisfactorily used as an excipient or filler for this type of tablet, and in addition it supplies calories or energy in a readily utilized form. Cornstarch is excellent as a disintegrator; in this study tablets were prepared with it that completely disintegrated in five to ten seconds. However, this speed of disintegration is not required in this instance, for ordinarily several minutes are required to raise the temperature of milk in an infant's nursing bottle from that of the household refrigerator to that of body temperature. In order to hold the components of a tablet in intimate contact, and to have the tablet retain its shape, a binder must be used. Materials satisfactory for this purpose are solutions of acacia, gelatin, or glucose. A lubricant is added to prevent the tablets from sticking in the commonly used rotary tablet machines. A number of materials, such as purified talcum, white mineral oil, calcium stearate, or dried starch, may be used for this purpose.

RESULTS AND DISCUSSION

The results of the seventy assays are reported in Table I. For the convenience of the reader, the samples have been arranged in the decreasing order of their reduced ascorbic acid content at the initial assay. Even though they were stored in darkness and at refrigerator temperature, each of the fourteen samples of enriched milk progressively lost reduced ascorbic acid (Table I). The average values for each of the five periods employed in this study were 84.8, 77.1, 69.0, 62.3, and 55.1 mg. of reduced ascorbic acid per liter, respectively.

Thus the average losses of reduced ascorbic acid were 9, 10, 8, and 8 per cent, respectively, for the four successive twenty-four-hour periods that the samples of enriched milk were stored under household conditions. These losses are small as compared to 31, 23, 14, and 9 per cent reported by Holmes[10] for losses of reduced ascorbic acid from unenriched pasteurized milk stored for similar periods under the same conditions. However, the relatively small losses observed in this study would not be applicable to commercially produced ascorbic acid-enriched milk, since the tested samples were prepared and stored under the most favorable conditions. Commer-

cially enriched milk would be subjected to unfavorable conditions during its delivery from the processing plant to the ultimate consumer. Bright light, particularly at summer atmospheric temperature, causes rapid destruction of reduced ascorbic acid in solution. Kon and Watson[11] exposed milk to June skyshine and found that all of its reduced ascorbic acid was destroyed within the first hour of exposure. Krauss[12] reported that pasteurized milk kept in a clear glass bottle at room temperature lost practically all of its reduced ascorbic acid within six hours. Holmes and Jones[13] exposed milk in commercial milk bottles to light that varied from a minimum intensity of 4.8 Gm. cal. per square centimeter to a maximum of 144.6 Gm. cal. per square centimeter and found that the reduced ascorbic acid was oxidized very rapidly, and that none remained after thirty minutes' exposure to bright sunshine.

It is evident from these observations that even if processors of commercial retail milk carefully enriched pasteurized milk for infant feeding to a definite standard of reduced ascorbic acid content, there would probably be a large and unknown loss of the reduced ascorbic acid between the preparation of the enriched milk and its ingestion by the infant. The loss would certainly be very significant if the bottled milk was allowed to stand for any length of time on the customer's doorstep exposed to bright light or sunshine.

TABLE I. STABILITY OF REDUCED ASCORBIC ACID IN MILK ENRICHED FOR INFANT FEEDING

SAMPLE	FIRST DAY MG./L.	SECOND DAY MG./L.	THIRD DAY MG./L.	FOURTH DAY MG./L.	FIFTH DAY MG./L.
1	88.9	81.4	73.4	66.8	60.3
2	88.7	80.2	73.2	64.5	59.0
3	87.6	80.5	72.5	64.8	57.1
4	87.4	81.0	72.5	65.3	58.3
5	87.0	78.5	70.9	64.6	59.1
6	86.6	77.3	67.1	60.9	53.6
7	85.9	77.3	68.7	64.7	58.7
8	85.4	76.3	66.5	64.7	53.3
9	83.5	74.6	65.3	57.4	48.4
10	83.4	78.0	69.8	61.5	54.3
11	83.1	75.0	67.9	59.8	51.3
12	82.3	74.4	65.7	58.5	50.4
13	79.6	74.4	68.6	61.4	56.4
14	78.4	70.0	63.7	57.8	51.1
Average	84.8	77.1	69.0	62.3	55.1

Also, it is not at all feasible in the average home to enrich milk for infant feeding. Very few mothers have the training, experience, or equipment to enable them to weigh accurately a tiny amount of crystalline ascorbic acid to add to the infant's nursing bottle. On the other hand, it would be a very simple procedure for a mother to add an ascorbic acid tablet to each nursing bottle as she takes it from the refrigerator and warms the milk that it contains to body temperature. Obviously, the tablet should be so manufactured that it will contain a standardized amount of ascorbic acid at the time it is dropped into the nursing bottle and will completely disintegrate and dissolve in somewhat less time than

is required for the temperature of the milk to rise from that of the refrigerator to that of body temperature.

Assuming an infant receives five feedings of modified milk every twenty-four hours (and the mother prefers to fortify all the milk), then each tablet designed for enriching the milk contained in a single nursing bottle should contain a minimum of one-fifth of an infant's daily requirement for reduced ascorbic acid. On the other hand, a tablet containing an infant's daily requirement of ascorbic acid could be added to a nursing bottle of modified milk, and the infant would receive its ascorbic acid in a single feeding, as when orange juice is fed. The breast-fed infant's requirements for ascorbic acid may be easily met by dissolving in water a tablet or tablets, depending upon whether daily or periodic feedings are preferred, and feeding the solution in place of orange juice.

It is generally accepted that synthetic ascorbic acid and the reduced ascorbic acid found in orange juice are identical in composition and chemical reactions. Several investigators have compared, with either human subjects or experimental animals, the nutritive value of equivalent amounts of synthetic ascorbic acid and reduced ascorbic acid which occurs in natural food materials. Everson and Daniels[14] concluded from studies with preschool children that comparable amounts of commercial ascorbic acid and ascorbic acid from food resulted in similar retentions. Hawley, Stephens, and Anderson[15] administered orange juice and ascorbic acid to four women and eight men and found that comparable amounts of ascorbic acid given orally as orange juice and as cevitamic acid resulted in similar urinary excretion curves. Todhunter and Fatzen[16] studied the utilization of ascorbic acid and reported that for equivalent amounts the urinary excretion and blood plasma levels of ascorbic acid were similar in the same subject when receiving vitamin C from red raspberries and from crystalline ascorbic acid. Elliott and Schuck[17] compared crystalline ascorbic acid with ascorbic acid in grapefruit in five studies using ten women and two men and found the results indicated approximately equal utilization of the ascorbic acid from the two sources. Einbecker, Jackson, Paul, and Ohlson[18] have stated that increases in plasma ascorbic acid obtained when crystalline ascorbic acid was ingested were greater than those obtained after the ingestion of strawberries. Hangartner and Gordonoff[19] concluded that when synthetic ascorbic acid in amounts corresponding to that in orange juice was fed to human beings and to rabbits there was no difference in the amount excreted. The American Medical Association[20] in commenting upon the utilization of ascorbic acid states synthetic ascorbic acid is absorbed and utilized by the body as well as that from natural sources.

The use of orange juice as a source of ascorbic acid to supplement milk in infant feeding involves frequent purchases of oranges and the expression of the juice. Furthermore, as noted above, orange juice prepared in this manner contains an unknown and variable amount of ascorbic acid, and thus there is not assurance that the infant is receiving enough ascorbic acid daily to meet its nutritional requirements. In con-

trast, the use of ascorbic acid tablets provides a means for easily feeding an infant a known amount of ascorbic acid daily.

SUMMARY

Since the amount of reduced ascorbic acid contained in milk is insufficient to meet the nutritional needs of a nursing infant, a supplementary source is required. Frequently orange juice expressed from oranges purchased from the local store is used as a source of ascorbic acid. Such orange juice contains an uncertain and variable amount of ascorbic acid. Tablets designed to disintegrate rapidly provide a convenient means for adding to the infant's nursing bottle of milk a standardized, uniform amount of ascorbic acid sufficient to meet daily nutritional requirements.

REFERENCES

1. Lorenz, A. J.: Personal communication, 1942.
2. Daniel, E. P., Kennedy, M. H., and Munsell, H. E.: Relative Vitamin C Content of Orange and Tomato Juices Determined Chemically and Biologically, J. Home Econ. **28**: 470, 1936.
3. Holmes, A. D., Pigott, M. G., and Tripp, F.: Comparative Costs of Vitamin C in Fresh and Commercially Canned Fruit and Vegetable Juices, New England J. Med. **225**: 68, 1941.
4. Holmes, A. D., Patch, J. A., and Tripp, F.: The Relation of Season, Weignt, and Price to the Vitamin C Content of Oranges, New England J. Med. **228**: 8, 1943.
5. Beacham, L. M., and Bonney, V. B.: Ascorbic Acid Content of Florida Citrus Fruits, J. Assn. Off. Agric. Chem. **20**: 517, 1937.
6. Harding, P. L., Winston, G. R., and Fisher, D. F.: Seasonal Changes in the Ascorbic Acid Content of Juice of Florida Oranges, Proc. Am. Soc. Hort. Sc. **36**: 358, 1939.
7. French, R. B., and Abbott, O. D.: Investigation of the Vitamin C Content of Florida Fruits and Vegetables. I. Effects of Maturation and of Cold Storage on the Vitamin C Potency of Oranges and Grapefruit, J. Nutrition **19**: 223, 1940.
8. Sharp, P. F.: Rapid Method for the Quantitative Determination of Reduced Ascorbic Acid in Milk, J. Dairy Sc. **21**: 85, 1938.
9. Holmes, A. D.: Rate of Destruction of Reduced Ascorbic Acid in Riboflavin-Fortified Pasteurized Milk, Food Tech. **4**: 92, 1950.
10. Holmes, A. D.: Comparison of the Stability of Reduced Ascorbic Acid in Raw and Pasteurized Milk, Amer. J. Dis. Child. **78**: 899, 1949.
11. Kon, S. K., and Watson, M. B.: The Effect of Light on the Vitamin C of Milk, Biochem. J. **30**: 2273, 1936.
12. Krauss, W. E.: Progress of Agricultural Research in Ohio, Ohio Agric. Expt. Sta. Bull. No. 617, p. 49, 1940.
13. Holmes, A. D., and Jones, C. P.: Effect of Sunshine Upon the Ascorbic Acid and Riboflavin Content of Milk, J. Nutrition **29**: 201, 1945.
14. Everson, G. J., and Daniels, A. L.: Vitamin C Studies With Children of Preschool Age, J. Nutrition **12**: 15, 1936.
15. Hawley, E. E., Stephens, D. J., and Anderson, G.: The Excretion of Vitamin C in Normal Individuals Following a Comparable Quantitative Administration in the Form of Orange Juice; Cevitamic Acid by Mouth and Cevitamic Acid Intravenously, J. Nutrition **11**: 135, 1936.
16. Todhunter, E. N., and Fatzen, A. S.: A Comparison of the Utilization by College Women of Equivalent Amounts of Ascorbic Acid (Vitamin C) in Red Raspberries and in Crystalline Form, J. Nutrition **19**: 121, 1940.
17. Elliott, K. J., and Schuck, C.: Utilization of Ascorbic Acid, J. Am. Dietet. A. **25**: 845, 1949.
18. Einbecker, B. L., Jackson, L., Paul, P., and Ohlson, M. A.: Ascorbic Acid in Strawberries as Measured by Blood Plasma of Women Following a Test Meal, Fed. Proc. **6**: 406, 1947.
19. Hangartner, J., and Gordonoff, T.: Excretion of Vitamin C in the Urine After Ingestion of Natural or Synthetic Vitamin C, Ztschr. Vitaminforsch. **12**: 226, 1942. (Chem. Abst. **37**: 420, 1943.)
20. Utilization of Ascorbic Acid, J. A. M. A. **136**: 402, 1948.

STUDY ON ORANGE JUICE, ORANGE JUICE CONCENTRATE, AND ORANGE PEEL OIL IN INFANTS AND CHILDREN

With Special Reference to Incidence of Dermatologic and Gastrointestinal Disturbances

C. L. Joslin, M.D., and J. E. Bradley, M.D.
Baltimore, Md.

VITAMIN C has long been recognized as one of the essential food elements in routine infant use, especially for the prevention of scurvy. More recently it has been shown that vitamin C is also necessary for the utilization of certain amino acetic acids,[1] as well as aiding in resistance to infections,[2] and the healing of wounds.[3] It is, of course, also intimately involved in vital developmental processes such as collagen formation,[4] mineral metabolism, and calcium utilization.[5]

Orange juice was extensively prescribed by physicians to provide vitamin C until the work of Waugh and King[6] and Svirbely and Szent-Györgyi[7] led to the synthetic production of ascorbic acid. There had long been a tendency for the laity as well as the medical profession to ascribe many undiagnosed disturbances in infancy to an allergic reaction from orange juice. Though the incidence of these reactions was never to our knowledge precisely determined, the substitution of ascorbic acid for orange juice in infant feeding in many cases became fairly common practice in some quarters.

From the Department of Pediatrics, University of Maryland.

We are indebted to Florida Citrus Commission for their grant-in-aid to conduct this investigation.

OBJECTIVES OF STUDY

It was thus decided to administer fresh orange juice and frozen orange juice concentrate to infants and children, and (1) to note the effect on the incidence of regurgitation, bowel movement, skin rashes, etc. It was also thought desirable (2) to skin test a number of both normal and eczematous infants and children for sensitivity to orange juice and orange peel oil; and (3) to determine the hydrogen-ion concentration of orange juice and orange peel oil. It was decided (4) to attempt to determine whether the time of administration of orange juice was related to the development of side actions, if any.

TEST SUBJECTS

The source of patients for study was from two infant homes and private pediatricians, a total of 406. Of this number, 338 were infants from 2 weeks to 2 years of age, and 68 were children ranging from 3 to 6 years of age.

The details of administration are shown in Table I. In all instances among this group the orange juice was well tolerated and enjoyed.

Institutional observations were made on 156 infants and on 68 older children, while 182 infants were ob-

TABLE I. 406 INFANTS AND CHILDREN GIVEN ORANGE JUICE

	AGE	AMOUNT GIVEN DAILY	DURATION OF OBSERVATION
Infants			
338	2 wk. to 2 yr.	¼ oz. at 2 wk. of age, ½ oz. at 4 wk. to 4 oz. at 1 yr.	8 to 12 mo.
Children			
68	3 to 6 yr.	4 to 8 oz.	2 to 6 mo.

served by practicing physicians—and followed from birth for a period varying from eight to twelve months.

pH VARIATIONS OF FROZEN AND FRESH ORANGE JUICE AND ORANGE PEEL OIL

Ideal gastric motility seems to function best under conditions that include as one of its essential components an optimal pH. Irritating substances when brought into contact with the gastric mucosa bring out alterations in pH. While the general qualitative effect of pH variation on the activity of smooth muscle[8] has been well established, recently the clinical significance of this effect as being responsible for the regurgitation of infants was suggested by the work of one of us.[9, 10, 11] Smooth muscle is very sensitive to alterations in the hydrogen-ion concentration.[12] An increased hydrogen-ion concentration produces a decrease in gastric motility, whereas a decreased hydrogen-ion concentration produces an increase in motility. Volatile substances are particularly prone to develop increased motility of the pyloric antrum.

TABLE II. DIFFERENCE IN pH AT 25° C.

Orange peel oil	5.65
Orange juice concentrate	3.76
Fresh orange juice extracted by household method without pressure upon orange peel	3.92
Fresh orange juice extracted by household method with moderate pressure upon orange peel	4.28

Note: It will be seen there is a considerable difference in the pH of orange juice properly prepared (3.76) and the pH of orange peel oil (5.65)

The pH was determined by use of a Beckman potentiometer. At 25° C. the pH of frozen orange juice concentrate was 3.76, of orange peel oil, 5.65. The pH of fresh orange juice prepared by halving the orange and extracting the juice by means of a Mixmaster was found to be 3.92 at 25° C. The pH of fresh orange juice extracted under moderate pressure being exerted on the skin was 4.28 at 25° C.

SKIN TESTS

The method of skin testing the infants and children was as follows: Patch tests were done by first cleansing the skin with acetone. A 3 mm. square of filter paper was laid on the skin, and the substance to be tested was applied with a toothpick. An Elastopatch protective covering was applied and permitted to remain in contact for forty-eight hours. At the end of this period the patch was removed and reaction noted. Substances used were 25 per cent solution of orange peel oil in olive oil and 25 per cent orange juice concentrate in olive oil.

Patch skin tests were made on 167 normal infants and children (with no known history of allergy) for sensitivity to orange juice and orange peel oil. The details of the testing are shown in Table III.

In addition, fourteen infants with eczema were skin tested with orange juice and orange peel oil. Three infants gave positive reactions to orange juice. Four infants gave positive re-

TABLE III. RESULTS OF SKIN TESTS ON 167 NORMAL INFANTS AND CHILDREN

	ORANGE JUICE (25% SOLUTION IN OLIVE OIL)	ORANGE PEEL OIL (25% SOLUTION IN OLIVE OIL)
Number of subjects negative to	164 (98.2%)	158 (94.6%)
Number of subjects positive to	3 (1.8%)	9* (5.3%)

Note: It will be noted that 98.2 per cent of infants and children gave no reaction to orange juice; 94.6 per cent gave no reaction to orange juice or orange peel oil; 1.8 per cent reacted to orange juice only; 5.3 per cent to orange peel oil.

*Included in this group were three who were positive also to orange juice.

actions to orange peel oil. Three infants gave positive reactions to both orange juice and orange peel oil. None of the infants with eczema were cured by the removal of orange juice from the diet. Four of the infants with eczema seemed to tolerate orange juice. In the remaining ten cases we were unable to evaluate the effect of orange juice because of the changing character of the eczema and the many other factors involved. However, three infants seemed to be irritated by the administration of orange juice.

CLINICAL MANIFESTATIONS OF SENSITIVITY

Of the 156 infants observed in the two institutions, the orange juice was well tolerated in every instance. There was no disturbance of bowel function (diarrhea or constipation) that could be attributed to the orange juice, and there was only a minimal amount of regurgitation. There were twenty-six infants who had transient rashes (maculopapular) that occurred during the test period. However, the eruptions occurred in every instance during the very hot weather, and, since they subsided with removal of orange juice from the diet and a change in the weather, it was thought the rash was related to the very hot weather, particularly as there was no recurrence of the rash when the infants were again given the orange juice.

Observations on the 182 infants followed in private practice were somewhat similar. No diarrhea or constipation attributable to the orange juice was noted. Six infants suffered from regurgitation, but five of these regurgitated all other food as well as the orange juice.

Seven infants of the private practice group of 182 cases developed a slight maculopapular rash on the face, which was thought to be due to the orange juice. However, four of these, when the orange juice was discontinued for a week and again given, had no rash. The three remaining infants developed slight rashes when the orange juice was repeated, and one infant broke out with maculopapular rash when synthetic ascorbic acid was given.

The older children all tolerated the orange juice and showed no side effects.

TIME OF ADMINISTRATION OF JUICE

It seemed that the most convenient time for administration of orange juice to the young infant was just before the usual morning bath about one-half hour before the mid-morning feeding. Most mothers preferred giving the orange juice at this time for the simple reason that, in giving the infant its first food other than milk, a certain amount is likely to be spilled, soiling the clothes. Also cod liver oil concentrate or A and D vitamins were added to the orange juice, and the combination was well tolerated.

With older infants and children, time of administration seemed unimportant.

AGE JUICE STARTED AND AMOUNT ADMINISTERED

The age at which the orange juice was started was at the beginning of the third week, two weeks being allowed for the infant to become adjusted to its formula or the breast feedings. The infants were given ¼ ounce of orange juice diluted with equal parts of water at the start, with the quantity increased gradually as is done with the formula or other foods. If this procedure is followed, the infant's tolerance for orange juice will be greatly enhanced.

METHOD OF PREPARING JUICE

Orange juice, when extracted without undue pressure being made on the orange peel, is well tolerated by infants and children and allergic reactions are minimal. Results in the two institutions provide a striking illustration of the importance of excluding orange peel oil from orange juice as far as possible. It is interesting to note that one institution at the beginning of the study reported that they had never had any difficulty or bad effects from giving fresh orange juice, while the second institution had discontinued the use of fresh orange juice because of the frequency of regurgitation and skin rashes, and had substituted synthetic ascorbic acid. Upon investigation as to the method of preparation of orange juice in the first institution, it was found that the juice was extracted by means of a Mixmaster which probably permitted only a minimal amount of peel oil to be mixed with the juice. Whereas, in the second institution, the juice was extracted by means of a mechanical extractor which exerted pressure on the skin of the halved orange—and hence there was a free mixing of peel oil and orange juice. Orange peel oil is known to contain about 90 per cent dextrolimonene and 10 per cent aldehydes, esters, and alcohols.

VITAMIN CONTENT

The total ascorbic acid content of fresh orange juice ranges from 34.8 to 45.3 mg. per 100 ml., and from 33.5 to 44.0 mg. per 100 ml. for canned.[13] For 65° Brix orange juice concentrate it is from 36.3 to 50.8 mg. per 100 ml., for the fresh raw juice of 42° Brix from 40.8 to 49.5 mg. per 100 ml., and after concentration and canning from 42.5 to 46.3 mg. per 100 ml. Retention of this content in fresh hand-reamed and machine-reamed orange juice has been calculated at 98.5 to 99.5 per cent[14] after twenty-four hours (either at room temperature or in a cold room at 40° F.), and at 95.8 to 96.4 per cent after one week when kept at 40° F. Our check of the ascorbic acid content of the frozen orange juice concentrate employed compared with the above figures, being 37.5 mg. per 100 ml.

SUMMARY

Three hundred ninety-two normal infants and children (from 2 weeks to 6 years of age) and fourteen eczematous infants (a total of 406) have been given orange juice for periods varying from 2 to 12 months, in amounts from ¼ ounce at 2 weeks of age to 8 ounces daily before meals. Seventy-five per cent of the infants were observed on orange juice for eight to twelve months.

pH studies of frozen orange juice concentrate, fresh orange juice (extracted by two different means), and orange peel oil have been made.

One hundred sixty-seven normal infants and children and fourteen eczematous infants have been skin tested with orange juice extract and with orange peel oil extract. Only 1.8 per cent of the normal cases were positive to orange juice; 5.3 per cent were positive to orange peel oil. The eczematous cases (as was to be expected) showed a higher positive reaction.

There was no disturbance of bowel function (diarrhea or constipation) that could be attributed to the orange juice. The incidence of regurgitation was minimal, as was also the development of rashes which could be specifically traced to orange juice ingestion. Five and three-tenths per cent of infants showed positive reactions.

It would thus appear that the method of preparation of the orange juice (i.e., maximal reduction of peel oil) is important. In young infants, graduated doses were administered for best results.

REFERENCES

1. Harris, L. J.: Vitamins in Annual Review of Biochemistry, vol. 4, Stanford University, Calif., 1935, Stanford University Press, p. 347.
2. Robinson, E. C.: The Vitamins and Resistance to Infection, Medicine **13**: 123, 1934.
3. Lanman, T. H., and Ingalls, T. H.: Vitamin C Deficiency and Wound Healing, Experimental and Clinical Study, Ann. Surg. **105**: 616, 1937.
4. Sherman, H. C.: Chemistry of Food and Nutrition, ed. 7, New York, 1946, The Macmillan Co.
5. Rose, M. S.: Rose's Foundation of Nutrition, ref. by MacLeod and Taylor, ed. 4, New York, 1944, The Macmillan Co.
6. Waugh, W. A., and King, C. J.: The Vitamin C Activity of Hexuronic Acid From Suprarenal Glands, Science **76**: 630, 1932.
7. Svirbely, J. L., and Szent-Györgyi, A.: The Chemical Nature of Vitamin C, Biochem. J. **27**: 279, 1933.
8. Gorman, R. A., Drier, J. D., and Rehfuss, M. E.: A Study of the Effect of Acids and Alkalis on Gastric Muscle Strips in the Rabbit, Am. J. Surg. **12**: 121, 1931.
9. Bradley, J. E.: Treatment of Epidemic Vomiting in Pediatric Practice, J. PEDIAT. **33**: 318, 1948.
10. Bradley, J. E., Proutt, L., Shipley, E. R., and Oster, R. H.: Evaluation of a Carbohydrate-Phosphoric Acid Solution in the Management of Vomiting, J. PEDIAT. **38**: 41, 1951.
11. Proutt, L. M., Shipley, E. R., Oster, R. H., and Bradley, J. E.: Study of the Effect of Hydrogen-ion Concentrations on Smooth Muscle Motility, Bull. School of Med. Univ. of Maryland **36**: 86, 1951.
12. Evans, C. L., and Underhill, S. W.: The Effect of Alteration of Hydrogen-ion Concentration on the Tone and Contractions of Plain Muscle, J. Physiol. **58**: 1, 1923.
13. Krehl, W. A., and Cowgill, G. R.: Vitamin Content of Citrus Products, Food Research **15**: 179, 1950.
14. Moore, E. L., Atkins, C. D., Wiederhold, E., and MacDowell, L. G.: Flavor and Ascorbic Acid Retention in Fresh Florida Citrus Juices, J. Home Econ. **37**: 290, 1945.

THE EFFECT OF SURGERY ON THE GROWTH OF PATIENTS WITH PATENT DUCTUS ARTERIOSUS

FORREST H. ADAMS, M.D., AND WILLIAM B. FORSYTH, M.D.*
MINNEAPOLIS, MINN.

SINCE the original report by Gross[1] of the first successful ligation of a patent ductus arteriosus in a patient with this congenital heart defect, a number of rather comprehensive reports on follow-up studies of patients who have had such surgery have appeared in the literature. The most recent report was by Gross[2] on the results on 412 patients operated upon by himself or members of his group.

Although the effect of ligation of the ductus arteriosus on the growth of children with such a defect has been alluded to briefly in a number of articles, no critical analysis has been made. In untreated patent ductus arteriosus Abbott[3] and Gross[4] found that their patients were usually of poor physique. In sixty-two patients, Shapiro[5] found thirty-two were normally developed, twenty-three were undersized, and six were obese. Gilchrist[6] and Benn[7] in England found comparable results. Following surgery, Gross[2] has stated that some children showed a considerable improvement in growth. No figures or criteria were given, however.

This report concerns the observations on the growth of sixty-one children with patent ductus arteriosus.

From the Department of Pediatrics, University of Minnesota.

This work was performed under a cooperative agreement between the University of Minnesota and the National Heart Institute, U. S. Public Health Service, Bethesda, Md.

*Alpha Phi Heart Research Fellow.

CLINICAL MATERIAL AND METHODS

All of the sixty-one children reported in this study were seen at the University Hospitals. In eight of these patients only preoperative observations were possible as either surgery was not performed or, if done, follow-up examinations were not done. Twenty-three of the patients were observed both preoperatively and postoperatively. Thirty children were seen for the first time by us at the time of admission to the hospital for surgery, thus only postoperative observations could be made on these children.

The criteria used by us for satisfactory observations on the growth of these children were as follows:

1. Preoperatively, at least two sets of data had to be taken six months apart.

2. Postoperatively, at least two sets of data had to be taken, one of which was at least one year after the surgery. We used the Wetzel "Grid for Evaluating Physical Fitness" for interpreting this data because of the comprehensive picture one obtains by its use when studying the height and weight in relationship to age. The criteria for satisfactory growth established by Wetzel were used in interpreting our data. The tolerance limits used were: ½ channel deviation per 10 levels of

progress, and 2 to 3 levels from the patient's own auxodrome in any one year.

RESULTS

Preoperative observations were available on thirty-one patients (eight preoperative only; twenty-three pre- and postoperative). As seen in Table I, preoperatively, there was a gain in physique by one individual, twenty-four had satisfactory progress, and six experienced a loss in physique. One experienced a gain in speed of growth, twenty-eight were satisfactory, and two had a reduction of speed of growth that was considered not to be satisfactory. In Table II is tabulated the lowest physique channel and the lowest auxodrome reached by each of the thirty-one children. Although the numbers are small, more children were of B_2 physique or lower than would be expected for children of our community. Likewise, more children had a reduced speed of growth than would be expected.

Postoperative observations were made on fifty-three children (twenty-three pre- and postoperative, thirty postoperative only). As seen in Table III, nineteen had a gain in physique, twenty-six experienced satisfactory progress, and eight had a loss in physique. There was a gain in speed of growth in nineteen, satisfactory progress was made by twenty-eight, and six had a reduction in the speed of growth.

TABLE I. EVALUATION OF PREOPERATIVE PHYSIQUE AND SPEED OF GROWTH

	GAIN	SATISFACTORY	LOSS	TOTAL NO. OF PATIENTS
Physique	1	24	6	31
Speed	1	28	2	31

TABLE II. PREOPERATIVE PHYSIQUE AND SPEED OF GROWTH DISTRIBUTION

Lowest Channel	A_4	A_3A_4	A_2MB_1	B_2	B_3	B_4	Total No. of patients
No. of Patients	0	5	15	6	1	4	31
Lowest Auxodrome	0-2%	2%	15%	67%	82%	98%	Total No. of patients
No. of Patients	1	2	10	8	4	6	31

TABLE III. EVALUATION OF POSTOPERATIVE PHYSIQUE AND SPEED OF GROWTH

	GAIN	SATISFACTORY	LOSS	TOTAL NO. OF PATIENTS
Physique	19	26	8	53
Speed	19	28	6	53

DISCUSSION

In some of our children with patent ductus arteriosus, the favorable effect of surgery on growth seemed fairly obvious as illustrated in Fig. 1. In other patients growth failure occurred following surgery as illustrated in Fig. 2. Percentagewise, however, more children had a gain in physique and an increase in rate of growth than would be expected normally. Likewise, the number of patients who had a loss in physique and/or a loss in speed of growth was small. The above

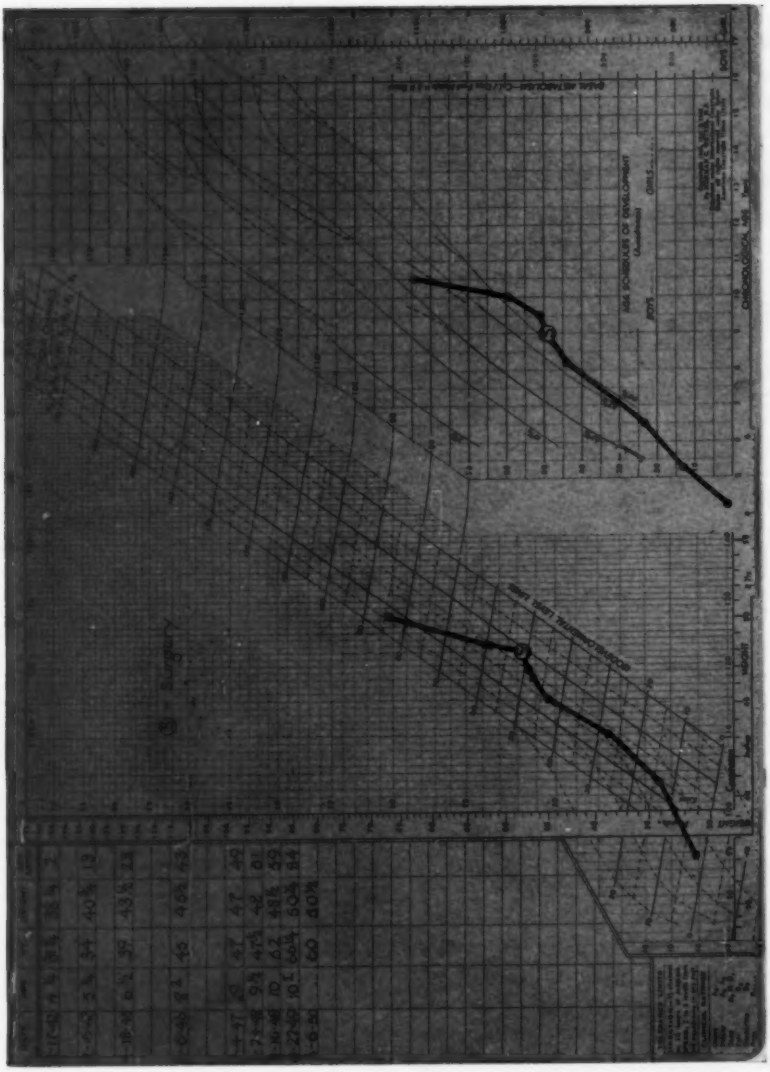


Fig. 1.

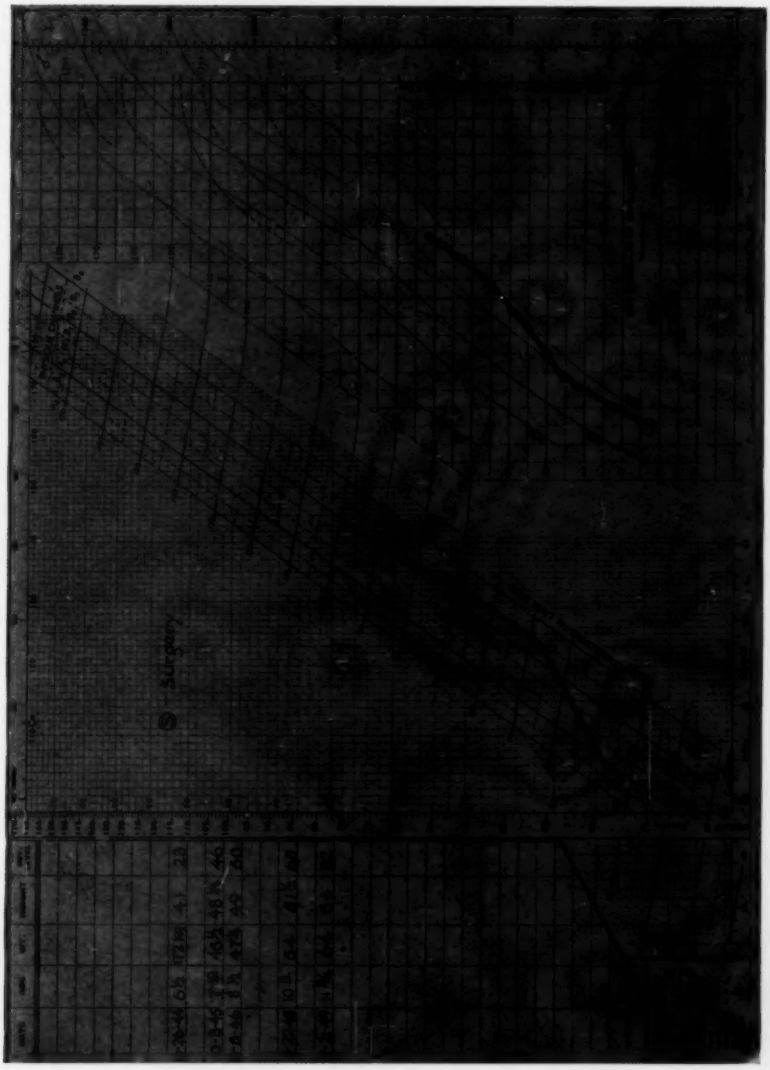


Fig. 2.

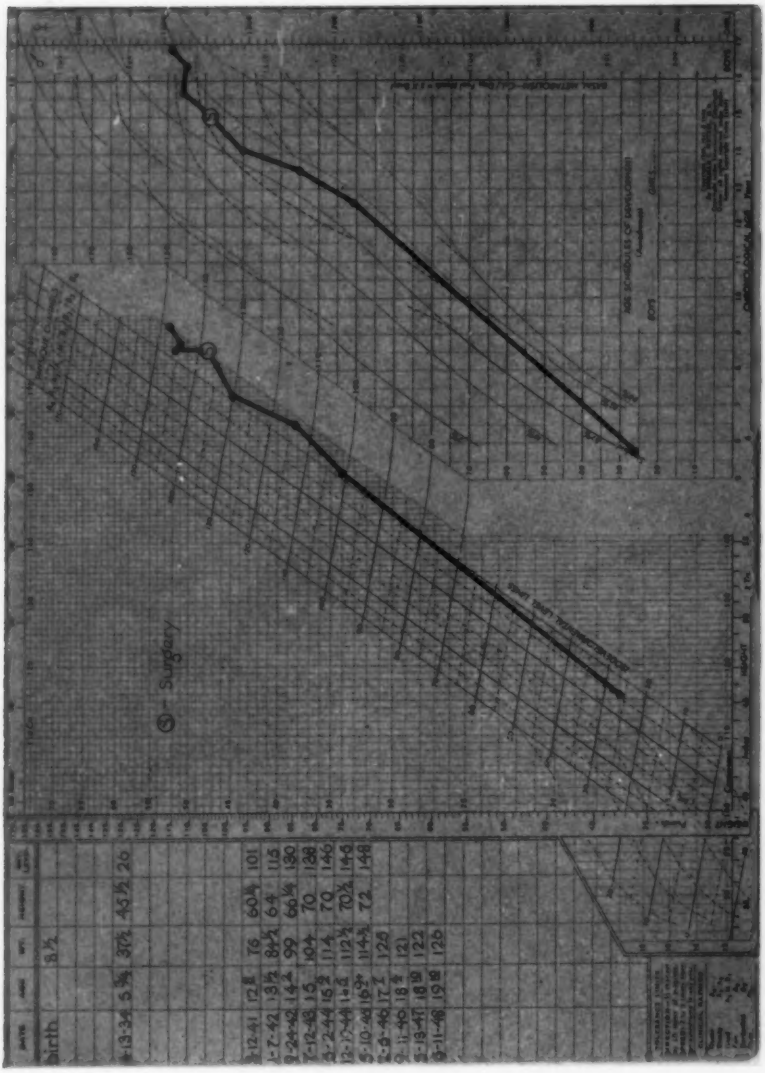

Surgery
birth 8½
+13-34 5 3/16 37½ 45½ 20
12-41 12 16 60¼ 101
1-7-42 13½ 64½ 115
9-24-42 14 99 60¼ 130
7-12-43 15 104 70 138
3-2-44 15½ 114 70 140
12-7-44 16 112¾ 70¼ 143
5-10-46 16¾ 114¾ 72 148
5-9-46 17 120
9-11-46 18¼ 121
5-13-47 18 19 122
9-11-48 19 8 126

Fig. 3.

figures do not show, however, that certain patients had a loss in physique and/or speed of growth preoperatively, and in those same patients if surgery was not performed until late in childhood the loss was not recovered. Such a patient is illustrated in Fig. 3.

The loss in physique and/or speed of growth following surgery can probably best be explained according to the following mechanisms:

1. Those conditions other than cardiac (infectious, metabolic, nutritional, or emotional) experienced by the population as a whole.

2. Persistent cardiac conditions (intra- or extracardiac defects and pulmonary hypertension).

In a previous communication[8] we demonstrated that at least a few patients with patent ductus arteriosus have pulmonary hypertension preoperatively. Cournand[9] has reported that one child followed by him with patent ductus arteriosus still had pulmonary hypertension five months after ligation of the patent ductus. Chapman[10] and Douglas[11] have demonstrated that pulmonary hypertension can become great enough in some instances to cause a reversal of the left to right shunt and the patient then becomes cyanotic. At post-mortem examination in such patients pathological changes have taken place in the pulmonary arterioles and arteries. These would seem to be of a permanent character. If pulmonary hypertension can persist following ligation of a patent ductus arteriosus, it could be a cause of persistent cardiac disability with resulting *growth failure*.

At the present time studies are under way to ascertain the importance of pulmonary hypertension in patent ductus arteriosus and also to determine the incidence of additional intra- or extracardiac defects. In a preliminary survey of fifty-six children with patent ductus arteriosus operated upon at the University Hospitals, twenty of the fifty-six children postoperatively had persistent heart murmurs, three of which had palpable precordial thrills. It is already known that several of these children have a persistent intracardiac defect as demonstrated by right heart catheterization.

SUMMARY

1. The growth of sixty-one children with patent ductus arteriosus has been evaluated using Wetzel's Grid.

2. Preoperatively more children were of the B_2 physique or lower than would be expected.

3. Preoperatively more children had a reduced speed of growth than would be expected.

4. Postoperatively more children had a gain in physique and an increase in speed of growth than would be expected.

5. In instances in which surgery was performed late in childhood, loss in physique or speed of growth was frequently not regained.

6. The possible causes of loss in physique or speed of growth following surgical ligation of the patent ductus arteriosus were discussed.

REFERENCES

1. Gross, R. E., and Hubbard, J. P.: Surgical Ligation of a Patent Ductus Arteriosus; Report of First Successful Case, J. A. M. A. 112: 729, 1939.
2. Gross, R. E., and Longino, L. A.: The Patent Ductus Arteriosus Observations from 412 Surgically Treated Cases, Circulation 3: 125, 1951.
3. Abbott, M., in Blumer's Bedside Diagnosis, 1929, Quoted by Benn (1947).

4. Gross, R. E.: Surgical Closure of the Patent Ductus Arteriosus, J. PEDIAT. 17: 716, 1940.
5. Shapiro, M. J.: Preoperative Diagnosis of Patent Ductus Arteriosus, J. A. M. A. 126: 934, 1944.
6. Gilchrist, A. R.: Patent Ductus Arteriosus and Its Surgical Treatment, Brit. Heart J. 7: 1, 1945.
7. Benn, J.: The Prognosis of Patent Ductus Arteriosus, Brit. Heart J. 9: 283, 1947.
8. Adams, F. H., Diehl, A., Jorgens, J., and Veasy, L. G.: Right Heart Catheterization in Patent Ductus Arteriosus and Aortic-Pulmonary Defect, Circulation, In press.
9. Cournand, A., Baldwin, J. S., and Himmelstein, A.: Cardiac Catheterization in Congenital Heart Disease, New York, 1949, Commonwealth Fund.
10. Chapman, C. B., and Robbins, S. L.: Patent Ductus Arteriosus With Pulmonary Vascular Sclerosis and Cyanosis, Ann. Int. Med. 21: 312, 1944.
11. Douglas, J. M., Burchell, H. B., Edwards, J. E., Dry, T. J., and Parker, R. L.: Systemic Right Ventricle in Patent Ductus Arteriosus: Report of a Case With Obstructive Pulmonary Vascular Lesions, Proc. Staff Meet., Mayo Clinic 22: 413, 1947.

FORMULA ROOMS FOR NEWBORN INFANTS IN LYING-IN HOSPITALS

Results of a Municipal Educational Program to Modernize Preparation of Formulas; With Special Reference to Terminal Sterilization

Helen M. Wallace, M.D., Harold Abramson, M.D., Margaret A. Losty, R.N., Michael Bade, Ph.G., and Leon Buchbinder, Ph.D.
New York, N. Y.

IN 1948, a preliminary discussion was presented by Wallace, Abramson, and Losty[1] of certain conditions under which formulas were prepared for newborn infants in lying-in hospitals of New York City. This study described the degree of supervision of personnel and procedures in formula rooms, the type of personnel employed, the amount of time devoted to preparation, and the method of terminal sterilization of formulas. The opinions of representative pediatricians, public health workers, nutritionists, and commercial formula companies were summarized with respect to the desirability of terminal sterilization. During the two years following this preliminary report, the New York City Department of Health has continued its educational compaign to raise the standards of hospital care of maternity patients and their newborn infants. One important phase of this program concerns the preparation of formulas. It is thought of interest to summarize in a progress report the results of our attempts to modernize procedures in preparing formulas for newborn infants and to describe the changes that have taken place.

From the New York City Department of Health, and the Department of Pediatrics, New York Medical College, Flower and Fifth Avenue Hospitals.

FORMULA PREPARATION IN LYING-IN HOSPITALS OF NEW YORK CITY

Definition of Terms.—By terminal sterilization is meant the application of moist heat to the final formula unit. This unit consists of the glass bottle into which has been poured the prescribed milk mixture and whose neck and lip have been sealed prior to terminal sterilization by a rubber nipple and then covered by a nipple cap or hood of either glass, metal, paper, or plastic construction.

Terminal sterilization may be accomplished by one of two recognized methods: (1) the high-pressure technique in which moist heat is applied to the formula unit at a temperature of 110° C. (230° F.) for ten minutes under a pressure of about 7 pounds in a mechanically sealed container; or (2) the low-pressure technique in which hot water and flowing steam are applied at a temperature of 100° C. (212° F.) for twenty-five minutes to the immersed formula unit in a closed water-vapor bath type of sterilizer. The comparative efficiency of both methods of sterilization has been published by Smith, Finley, Wright, and Louder[2] and by Finley, Smith, and Louder.[3]

In the preliminary handling of utensils, a "clean" technique may be car-

ried out as recommended by the American Hospital Association.[4] With this method, all utensils, rubber nipples, formula bottles, and nipple caps receive a thorough scrubbing and washing so as to be rid of foreign particles. The nipples are then boiled. The formulas are mixed and handled in a manner to prevent soiling and are poured into the formula bottles to which are applied the rubber nipples and nipple caps. Terminal sterilization of the formula unit is then carried out to assure a product free from contamination. This method of formula preparation using a "clean" technique and then terminal sterilization has several advantages over an "aseptic" technique which entails preliminary sterilization of equipment and surgical technique in preparation; the latter procedure is, however, advisable in the preparation of formulas composed of ingredients which cannot withstand the heat of terminal sterilization. The advantages of the "clean" technique are that it is less time-consuming and that it is more readily adapted for use by personnel in formula rooms.

General Remarks on Methods of Terminal Sterilization Adopted in City of New York.—In 1947, only 27 per cent of the lying-in hospitals employed terminal sterilization. By 1949, this percentage increased to 83, with the use by 80 per cent of these hospitals of the high-pressure technique (Table I). This result may be due in part to installation by the hospitals of autoclaves designed for high-pressure sterilization, before observations had been completed on the comparative efficiency of apparatus constructed for low-pressure technique.[2, 3]

Two hospitals are still applying a rubber bottle cap to the formula bottle immediately after filling the latter with the milk mixture. A rubber feeding nipple is then substituted for the bottle cap just prior to feeding time. It is, of course, difficult in this type of procedure to maintain sterility because of excessive handling of the feeding nipple.

TABLE I. COMPARISON OF METHODS OF TERMINAL HANDLING OF FORMULAS IN HOSPITAL GIVING LYING-IN CARE IN NEW YORK CITY, 1947 AND 1949

TYPE OF FORMULA PREPARATION	1947		1949†	
With terminal sterilization		30		86
With pressure	10		67‡	
Without pressure	20		18	
Type unknown			1	
*Without terminal sterilization**		83		18
Method No. 1	69		8	
Method No. 2	0		8	
Method No. 3	14		2	
Totals		113	104	
Per cent with terminal sterilization		27		83

**Method No. 1* consists of the use of an "aseptic technique" in formula preparation, with immediate application to the bottle of a nipple and a nipple-cap after formula has been poured into individual bottle.

**Method No. 2* consists of the use of a "clean technique" in formula preparation, with previously sterilized equipment and with immediate application to the bottle of a nipple and nipple-cap after the formula has been poured into individual bottle.

**Method No. 3* consists of the use of an "aseptic technique" in formula preparation, with the immediate application of a rubber cap to formula bottle immediately after the formula is poured; the rubber cap is subsequently removed and a nipple applied.

†In the two-year interval, seven hospitals discontinued their maternity and newborn services. This report covers 104 of the current 106 hospitals with maternity and newborn services in New York City.

‡Included are six hospitals which are securing formulas from a commercial formula laboratory.

TABLE II. TERMINAL STERILIZATION OF FORMULAS IN NEW YORK CITY ACCORDING TO SIZE OF MATERNITY SERVICE IN 1949

SIZE OF MATERNITY SERVICE	TOTAL NO. HOSPITALS	TERMINAL STERILIZATION			NO TERMINAL STERILIZATION			TOTAL NO. HOSPITALS WITHOUT TERMINAL STERILIZATION	% HOSPITALS WITH TERMINAL STERILIZATION
		PRESSURE	NON-PRESSURE	UNKNOWN	ASEPTIC TECHNIQUE	CLEAN TECHNIQUE	RUBBER CAP, THEN NIPPLE		
Under 20 beds	17	15	1		1			1	94
20-49 beds	59	40	8	1	5	3	2	10	83
50-79 beds	18	10	4		2	2		4	78
80-109 beds	5	2	1			2		2	60
110 beds and over	5	1	3		1			1	80
Totals	104	68	17	1	9	7	2	18	83

Methods Used According to Size of Maternity Service.—A comparison of 1947 and 1949 shows that hospitals with all sizes of maternity service adopted terminal sterilization for formulas as follows: 94 per cent of hospitals with less than 20 maternity beds in 1949 as compared with 9 per cent in 1947; 83 per cent of hospitals with 20 to 49 maternity beds in 1949 as compared with 29 per cent in 1947; 78 per cent of hospitals with 50 to 79 maternity beds in 1949 as compared with 31.6 per cent in 1947; 60 per cent of hospitals with 80 to 109 maternity beds in 1949 as compared with 20 per cent in 1947. There was very little change in the hospitals with more than 109 maternity beds, 80 per cent using terminal sterilization in 1949 as compared with 75 per cent in 1947 (Table II).

One of the reasons for the lag in adoption of terminal sterilization by the very large maternity hospitals may be due in part to the educational program of the Department of Health that was primarily geared to hospitals with the smaller maternity services. Some of the larger hospitals expressed the need for additional time to study available literature. Consideration was given to the relative efficiency of both methods of terminal sterilization, with respect to personnel and the objectives to be achieved.

Method of Collection of Feeding Formulas and Rubber Nipple Samples for Bacteriological Culture.—The ultimate aim in preparation of formulas is the production of a safe product for the infants, as gauged by present methods of bacteriological cultures and physicochemical determinations. Observations on the effect of terminal sterilization on the heat-labile nutrients of infant formulas have been published by Hodson.[5]

Investigations on the safety of formulas for infants by the New York City Department of Health are based on the determination of bacterial counts of the formulas and of nipple rinses, and on the detection of a group of organisms, the so-called coliform organisms, an accepted indicator of contamination. The American Hospital Association[4] has recommended weekly bacteriological cultures as a minimal requirement. Hospitals giving maternity care in the City of New York are encouraged to adopt the performance of weekly bacteriological cultures, in addition to the annual sampling of formulas and nipples, as is carried out by the Department of Health.

Bacteriological sampling of infant formulas is an unusual and recent activity in many health departments. A detailed description is therefore presented of the technique used and the equipment that has been elaborated by obtaining cultures of formulas and rubber nipples.

Formula and Nipple Procedure:

1. Inspector washes his hands before taking samples.
2. Before entering formula room or nursery, the inspector dons a sterile cap, gown, and mask.
3. *Formula samples* are taken in a complete unit of bottle, nipple, and nipple cap, as found and used in the hospital.
4. The neck of the formula bottle, including the nipple and/or cap, is covered with previously sterilized aluminum foil. The aluminum foil is pressed around the nipple cap and the neck and shoulders of the bottle so as to prevent dislodging of the cap in transit.
5. If nipples are stored in sterile containers in nursery, two nipples are

taken from the bottom of the nipple container and submitted as a composite sample. The nipples are placed in a sterile sample bottle by means of sterile forceps, care being taken not to touch the neck of the bottle.

6. If nipple container is not used, the nipple sample is taken from a completed formula unit by means of sterile forceps. In this case, one nipple constitutes a sample, provided that a second bottle is not available.

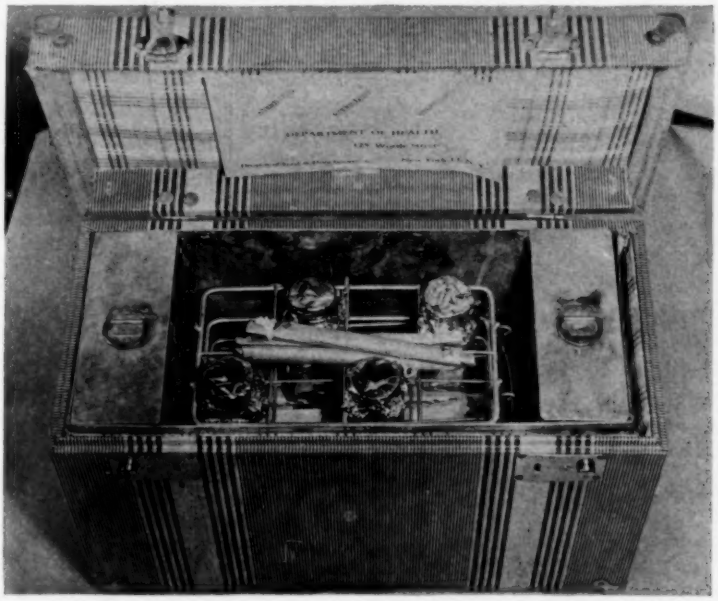


Fig. 1.—Refrigerator carrying bag used to transport formula and rubber nipple samples for bacteriological cultures from maternity hospital to the laboratory.

7. All samples are transported in a refrigerator carrying bag in such a manner as to prevent tipping (Fig. 1).

Equipment Used:

A refrigerator sample bag for transportation of formula and nipple samples from the hospital to the Department of Health laboratory was designed and constructed.*

This insulated sample bag is of the airplane luggage type, constructed of plywood, with a hinged cover, metal reinforced corners, metal locks and hinges, and carrying handle on cover. The entire inside of the case, including the cover, is insulated with approximately ¼ inch thickness of fiber-glass wool insulating material. The inside surface of the bag is covered with a durable cloth. Inside measurements are 16¾ inches long by 7¼ inches wide by 10¾ inches high. A copper box fits snugly into the interior of the sample bag. Inside measurements of copper box are 16½ inches long by 7 inches wide by 10½ inches high.

The copper box is equipped with two removable copper ice containers with tight-fitting covers and held in place at each end with stops. The size of the ice containers is such as to permit sample storage space of the following dimensions: 11½ inches long by 7 inches wide by 10½ inches high.

The ice containers are filled with either cracked ice or dry ice. An eight-

*This refrigerator sample bag was designed by Mr. Michael Bade.

TABLE III. RESULTS OF BACTERIOLOGICAL CULTURES OF FORMULAS TAKEN IMMEDIATELY AFTER FORMULA PREPARATION

TYPE OF FORMULA PREPARATION	NO. OF SAMPLES	NO. OF SAMPLES UNSATISFACTORY	PER CENT SATISFACTORY
With terminal sterilization	108	8	93
Pressure	80	6	93
Nonpressure	26	2	92
Type unknown	2	0	100
Without terminal sterilization	23	4	83
Method No. 1	11	1	91
Method No. 2	10	2	80
Method No. 3	2	1	50

TABLE IV. RESULTS OF BACTERIOLOGICAL CULTURES OF FORMULAS TAKEN TWENTY-FOUR HOURS AFTER FORMULA PREPARATION

TYPE OF FORMULA PREPARATION	NO. OF SAMPLES	NO. OF SAMPLES UNSATISFACTORY	PER CENT OF SAMPLES SATISFACTORY
With terminal sterilization	101	14	86
Pressure	74	10	86
Nonpressure	26	4	85
Unknown	1	0	100
Without terminal sterilization	22	5	77
Method No. 1	9	2	78
Method No. 2	11	2	91
Method No. 3	2	1	50

TABLE V. RESULTS OF BACTERIOLOGICAL CULTURES OF RUBBER NIPPLES TAKEN IMMEDIATELY AFTER FORMULA PREPARATION

TYPE OF FORMULA PREPARATION	NO. OF SAMPLES	NO. OF UNSATISFACTORY SAMPLES	PER CENT OF SAMPLES SATISFACTORY
With terminal sterilization	108	25	77
Pressure	80	20	75
Nonpressure	27	5	81
Unknown	1	0	100
Without terminal sterilization	22	8	63
Method No. 1	13	4	69
Method No. 2	9	4	56

TABLE VI. RESULTS OF BACTERIOLOGICAL CULTURES OF RUBBER NIPPLES TAKEN TWENTY-FOUR HOURS AFTER FORMULA PREPARATION

TYPE OF FORMULA PREPARATION	NO. OF SAMPLES	NO. OF UNSATISFACTORY SAMPLES	PER CENT OF SAMPLES SATISFACTORY
With terminal sterilization	101	25	76
Pressure	78	19	76
Nonpressure	22	6	73
Unknown	1	0	100
Without terminal sterilization	20	7	65
Method No. 1	10	3	70
Method No. 2	10	4	60

compartment, steel wire carrying rack is used in the sample bag to keep sample bottles upright and prevent leakage.

A detailed check of the sampling bag has shown that it is possible to maintain temperature below 50° F. in the interior of the bag with cracked ice, regardless of the outside temperature, for the period of time necessary to transport samples from a hospital at any point in the city to the Department of Health laboratory.

Results of Bacteriological Cultures of Formulas and Rubber Nipples.— During 1949, the Department of Health collected formula and nipple samples in the above manner for bacteriological testing by its own laboratories. The American Hospital Association[4] has recommended the standard count of 25 bacteria per milliliter as the upper limit of safety for a formula sample. This standard has been adopted in New York City. No similar standard has been set for bacteriological testing of nipples, which obviously is significant omission. The Department of Health has tentatively set a working standard of 25 bacteria per milliliter of nipple rinse, pending further studies.

The results of bacteriological cultures of formula samples and of nipple samples are shown in Tables III, IV, V, and VI. A consistently higher percentage of satisfactory bacteriological results is noted in hospitals using terminal sterilization of formulas. When the data of Tables III, IV, V, and VI are combined into one over-all table, the difference between the terminal sterilization and nonterminal sterilization method is statistically significant.* The high-pressure and low-pressure techniques of terminal sterilization gave comparable results.

These findings are, however, subject to the limitations of small number of samples cultured and to the unselected method of securing the samples.

*The data were tested for statistical significance by Miss Vivian Pessin, Senior Statistician, New York City Department of Health.

DISCUSSION

Several facts are brought out by this study: (1) the favorable effect of a municipal health department's educational program on the adoption of modern formula procedures by hospitals giving maternity care; the recommendations advanced by the American Hospital Association[4] and by the American Academy of Pediatrics[6] have undoubtedly aided such a program; and (2) the significantly satisfactory bacteriological results that were obtained by a formula technique with terminal sterilization as compared to one without this final procedure.

It is recognized that the results of bacteriological cultures constitute only one criterion of the safety of a formula. Possibly virus and fungus cultures should also be made. Davis[7] states, however, that use of moist heat is the method of choice in sterilization. It is rapid, and the vegetative cells of all pathogenic bacteria, as well as fungi and viruses, are sterilized within a few minutes at temperatures of 50° to 70° C. (122° to 158° F.). Even the much more resistant spores of the anthrax bacillus and other pathogens are all sterilized within a few minutes at 100° C. (212° F.). The rate of killing by moist heat increases several hundred fold with each increase in temperature of 10° C. (21° F.).

Some thermophilic saprophytes have the property, however, of surviving and even multiplying rapidly at levels as high as 80° C. (176° F.); their

spores may survive boiling for twenty-four hours. Because of the resistance of the spores of various anaerobes it is usual practice to expose material to steam at a temperature of 120° C. (248° F.) for twenty to thirty minutes.

However, the question arises whether it is necessary to use moist heat at such high temperatures for the terminal sterilization of milk. Since all known pathogens, viruses, and fungi are destroyed within a few minutes at temperatures of 50° to 70° C. (122° to 158° F.), it would seem that for purposes of terminal sterilization of milk formulas the low-pressure technique at 100° C. (212° F.) for twenty-five minutes would suffice. As far as is known, the survival of spore-bearing organisms does not seem to be a problem in connection with the spread of communicable disease among newborn infants. This aspect of the subject merits further study.

The observations of Hodson[5] indicate that formulas for infants that were subject to low-pressure terminal heating showed an average retention of 95 per cent of the ascorbic acid, 91 per cent of the thiamine, and 100 per cent of the lysine. Similar samples exposed to high-pressure terminal heating showed an average retention of 97 per cent of the ascorbic acid, 91 per cent of the thiamine, and 100 per cent of the lysine. Hodson concluded that the small losses of the three relatively heat-labile nutrients indicate that no significant loss occurs of the more heat-stable nutrients of milk during terminal sterilization. The nutritional qualities of the diluted milk-carbohydrate mixtures are therefore altered only slightly.

According to the report of the American Hospital Association,[4] the only advantage of the high-pressure, high-temperature type of sterilization is that a greater percentage of sterile formulas results because some varieties of spores are killed. However, this process requires more skilled personnel and is more expensive to operate. Furthermore, in contrast to Hodson, there is the added risk of physical and chemical damage to the formulas. Other disadvantages are present such as caramelization of milk, "boiled" flavor taste of the milk, breakage of equipment if the autoclave is opened too soon before equalization of inside and outside pressure, clogging of the nipple openings if the bottles are overfilled, and more rapid deterioration of the rubber nipples. Future refinements in equipment and in technique may, however, overcome these disadvantages.

By contrast, the nonpressure type of sterilization is simpler and less expensive to operate. The same apparatus may also be used to cool formulas by draining the hot water in the tank and by replacing it with circulating cool water. In addition there is avoidance of nutritive and physical damage to the formulas. The method is safe bacteriologically. Over 50 per cent of the formulas are rendered sterile; while the remainder gives a bacterial count uniformly less than 10 colonies per 5 ml. of milk.

In the final analysis, however, the efficacy of either method of terminal sterilization of formulas will be determined by long-term observations on the prevention of outbreaks of diarrheal and respiratory diseases, and disorders such as thrush. It may eventually be found, for example, that the present

disadvantages of high-pressure sterilization are greatly outweighed by the important factor of safety in the prevention of the spread of communicable disease in the nurseries of lying-in hospitals. Finally, it must not be construed that terminal sterilization of formulas will alone accomplish the desired objectives. Attention to other medical and nursing policies and procedures must be given their due weight.

SUMMARY

Tentative impressions are presented on the results of a continuous program from 1947 to 1949 by the Department of Health of New York City to modernize the preparation of feeding formulas for newborn infants in hospitals giving maternity care in the prevention of infection. Terminal sterilization of formulas is discussed and a method is described of sampling the formulas and rubber nipples for bacteriological cultures.

REFERENCES

1. Wallace, Helen M., Abramson, H., and Losty, Margaret A.: Formula Rooms for Newborn Infants in Lying-in Hospitals: A Preliminary Study on Supervision and Certain Technics for Preparation, Pediatrics **1**: 758, 1948.
2. Smith, F. R., Finley, R. D., Wright, H. J., and Louder, E. A.: Terminal Heating of Infant Formula: I. Bacteriological Investigation of Low-Pressure Technique, J. Am. Dietetic A. **24**: 755, 1948.
3. Finley, R. D., Smith, F. R., and Louder, N. A.: Terminal Heating of Infant Formula: II. Bacteriological Investigation of High-Pressure Technique, J. A. Dietetic A. **24**: 760, 1948.
4. Procedures and Layout for the Infant Formula Room, American Hospital Association, Chicago, Ill., 1949.
5. Hodson, A. Z.: Terminal Heating of Infant Formula: III. Retention of Heat-Labile Nutrients, J. Am. Dietetic A. **25**: 119, 1949.
6. Standards and Recommendations for Hospital Care of Newborn Infants, Committee on Fetus and Newborn, American Academy of Pediatrics, Nov. 18, 1948.
7. Davis, B. D., in Dubos, R. J.: Principles of Sterilization, in Bacterial and Mycotic Infections in Man, Philadelphia, 1948, J. B. Lippincott Co., p. 637.

Case Reports

PERIARTERITIS NODOSA IN INFANCY

Report of a Case Following Allergic Reactions to Penicillin

Lester Adelson, M.D.
Cleveland, Ohio

THE occurrence of periarteritis nodosa (synonyms: polyarteritis,[1, 2] panarteritis,[1] polyarteritis nodosa,[3, 4] necrotizing arteritis,[5] primary arteritis,[6] essential polyarteritis[7]) in childhood is an infrequent event. Rothstein and Welt[8] in 1933 collected from the literature twenty-one cases in children up through the age of 15 years and added two of their own. These twenty-three cases comprised 11.8 per cent of 195 cases in all age groups found by these authors. Following the appearance of this comprehensive review, individual case reports continued to appear,[4, 5, 9, 10, 11] and by 1941 the number of cases in the juvenile age group had risen to forty-four.[6] Since that time the incidence of the disease appears to have increased, and childhood periarteritis nodosa has been described by a number of observers within the past decade.[3, 12, 13, 14, 15, 16, 17, 18] The more frequent diagnosis of periarteritis nodosa in childhood was felt by Rothstein and Welt[8] to be due not to a greater incidence of the disease but rather to a more widespread and thorough knowledge of its characteristics and to more careful and complete microscopic examination at autopsy. Other authors[14, 19] feel that there has been a real increase in the number of cases.

In infants under one year of age periarteritis nodosa is rare. But two of the twenty-three cases reported by Rothstein and Welt[8] fell into this early age group. Search of the recent literature disclosed only three additional cases in the first year of life.[12, 13] Recently, a 4-month, 13-day-old white male came to autopsy at the Cuyahoga County Coroner's Office and disclosed severe classical periarteritis nodosa. A careful anamnesis furnished by intelligent and observing parents pointed toward a fairly definite allergic basis as the probable major etiological factor. Because of the paucity of infantile cases and because the details of the child's illness strongly indicate a probable hypersensitivity to (oral) penicillin as the responsible agent, it is felt that the case is worthy of report.

CASE REPORT

V. B. Jr., a 4½-month-old white male, was brought to the Cuyahoga County Morgue with a history of having expired suddenly and unexpectedly at home.

Past History—The child had been delivered normally following an uneventful gestation. Labor had been induced one week prior to the expected date of delivery because eclampsia had developed during the mother's one previous pregnancy two years earlier. At that time mounting hypertension, ankle edema, and albuminuria had indicated the advisability of interrupting pregnancy at 7½ months. Labor was artificially started and resulted in the birth of a premature infant who survived one day. Three post-partum convulsions occurred, followed by complete maternal recovery. Ankle edema and albuminuria disappeared, and the blood pressure came down to a normal level where it had remained

From the Laboratory of the Cuyahoga County Coroner's Office.

consistently. The last normal menstrual period occurred in the latter part of January, 1950, and V. B. Jr. was born on Nov. 1, 1950. His birth weight was 5 pounds, 3 ounces, and he left the hospital at the end of a week weighing 5 pounds, 1 ounce. He was started on breast feeding, supplemented by an Olac formula. At the end of four weeks the breast feedings were discontinued, and he was maintained on Olac alone. At six weeks ADC, 5 drops a day, was started, and at ten weeks dry cereal and strained fruit and vegetables were added. For a brief interval of several days at age seven weeks a new formula of evaporated milk and Dextri-Maltose was tried, but it was soon discontinued, and he was returned to his original diet. During the entire period prior to the onset of his present illness he had always appeared well, developed normally, and gained weight progressively. At two weeks he weighed 6 pounds, at 6 weeks 9 pounds, 15 ounces, at ten weeks 14 pounds, 2 ounces, and at eighteen weeks, five days prior to his death, 16 pounds, 10 ounces.

Family History.—Both parents were living and well. The father was 38 years old and the mother 33 years at the time of conception. The maternal grandmother was living with hypertension and "sinusitis." The maternal grandfather was living and well. One maternal aunt was said to have died of subacute bacterial endocarditis at 31 years of age following rheumatic fever. Both paternal grandparents were dead, the grandmother having died at 68 with carcinoma of the breast, and the grandfather having been shot during the late war. There was no history in the grandparents, the parents, or the parents' siblings of any allergic diseases or manifestations save for the "sinusitis" previously noted. No familial illnesses of any type were brought out by questioning.

Present Illness.—On Feb. 19, 1951 the mother noted that the child was feverish with a rectal temperature of 102° F. There was slight cough but no rhinorrhea. A moderate degree of cervical adenopathy was noted which persisted throughout the course of the illness. The child was started on 0.62 gr. of aspirin every four hours while awake, and this was continued during the first two weeks of his illness, during which he received a total of 31 1¼ gr. tablets (38.75 gr.) By the next day the temperature had risen to 104° F. The child was examined by a pediatrician who prescribed oral penicillin, 50,000 units every four hours. Twenty-four hours following the institution of penicillin, a discrete punctate and macular rash was noted on the diaper area and within a day it had appeared on the face, ears, back, and legs, meanwhile becoming confluent. The temperature continued steadily elevated at 103° to 104° F., and it was felt that the penicillin might be responsible for both the rash and the fever. It was therefore discontinued after 12 tablets (600,000 units) had been given. The eruption was treated locally with baking soda compresses and a lotion, and it faded within thirty-six hours after the cessation of penicillin. A slight nasal discharge appeared, and Neo-Synephrine, 0.25 per cent, was instilled intranasally thrice daily for several days, until the nose no longer discharged. Meanwhile the child was started on Eskadiazine (1 dram, 5 c.c., contains 7½ gr. of sulfadiazine), one-half teaspoon every four hours. On February 26 the Eskadiazine was stopped after having been given for one day, and penicillin was begun once more. Within forty-eight hours a purplish blotchy eruption appeared over the entire face, trunk, and extremities, accompanied by severe conjunctival injection and lacrimation and increased swelling of the cervical glands. The penicillin was once more discontinued after 10 tablets had been given. (The total penicillin administered was 22 tablets or 1,100,000 units.) The eruption started to fade

within seventy-two hours. During this phase of the illness the temperature was maintained steadily at 102° F., and there were frequent episodes of diaphoresis. On March 3 typical urticarial wheals and dermatographia made their appearance. On March 5 the child was started on Benadryl, ⅓ capsule in his formula every four hours. By March 8 the temperature was normal for the first time since the onset of the illness seventeen days previously, and the child was taken to the pediatrician's office where the only abnormality found was the presence of hives. Clinically, he appeared to have completely recovered from his respiratory infection. Despite the administration of the Benadryl, the hives persisted, and the medication was discontinued on March 9 following two episodes of vomiting, the only such episodes occurring during the entire illness. Syrup of Histadyl (1 c.c. equals 6 mg. thenylpyramine fumarate), 5 to 10 drops every four hours, was substituted. By March 10 the hives were completely gone. Because it was felt that the child might be allergic to his formula, he was tried on evaporated milk and Allerdex from March 9 to 11, and then he was put back on Olac. During the entire period of illness he had taken his feeding well and gained weight. On March 12 he started to refuse his bottle and began to lose ground. The next day, his temperature rose to 102° F., and a 50 mg. Chloromycetin capsule was inserted into his rectum, followed by a second capsule in four hours. Following a small poorly-taken evening feeding the child dozed fitfully for a brief interval and then suddenly screamed, became rigid and cyanotic, gasped, and became comatose. Resuscitative efforts by the local fire department with oxygen and carbon dioxide were futile, and the child expired within a few minutes, twenty-two days after the onset of his illness.

Autopsy.—

Gross Examination: External examination disclosed a well-developed and well-nourished white male infant weighing 15½ pounds and measuring 26 inches from crown to heel. The only noteworthy external feature was the presence of bilateral hydroceles. Internally, the most striking lesions were located in the heart and lungs. The *heart* was enlarged in all diameters and presented multiple subendocardial petechiae on the anterior and posterior surfaces. All the major branches of both coronary arteries stood out prominently and presented a conspicuously nodular "beaded" appearance. The vessels were firm to palpation and on cross section showed markedly narrowed lumina except for an aneurysmal dilatation filled with clot in the left circumflex branch. The myocardium was uniformly pale brown and showed no gross evidence of infarct. The ductus arteriosus was closed and there were no congenital cardiac anomalies. The *lungs* were heavy and subcrepitant. Their cut surfaces were deep purple-red and revealed foci of grayish consolidation. Voluminous quantities of bloody frothy fluid exuded on pressure. The *thymus* displayed multiple petechiae beneath its capsule. The remainder of the gross examination was not remarkable.

Microscopic Examination: Multiple sections taken from all portions of the heart disclosed a severe necrotizing arteritis and arteriolitis characteristic of periarteritis nodosa. All the stigmas of the disease were present, e.g., fibrinoid necrosis and edema of the media, extensive inflammatory infiltration in the adventitia and media, aneurysm formation with thrombosis, and intimal proliferation with obliteration of the lumen. In no area was the myocardium infarcted as a result of the vascular disturbance. The veins were not involved by the inflammatory process. In some of the diseased vessels only a sector of the wall was damaged, in others the entire circumference was destroyed. Similar necrotizing and proliferative

changes were seen in the *mesenteric arteries* and in the arteries and arterioles of the *peri-adrenal fat*, the *epididymis*, *prostate*, and *testis* (Fig. 1). The arteries and arterioles in all the other organs of the body including the kidney were completely normal.

The *lungs* were the seat of an extensive bilateral interstitial pneumonia, with pulmonary congestion, edema, and chronic peribronchitis. The mesothelial serosal cells on the pleural surface of the *diaphragms* showed swelling and proliferation with the formation of multinucleated giant cells. In the *ileum* there were focal zones of ulceration with marked inflammatory infiltration into the submucosa. The sinuses of the *abdominal lymph nodes* and the *spleen* were filled by an extensive pleomorphic cellular exudate, and there was necrosis of the reticulum cells of the germinal follicles.

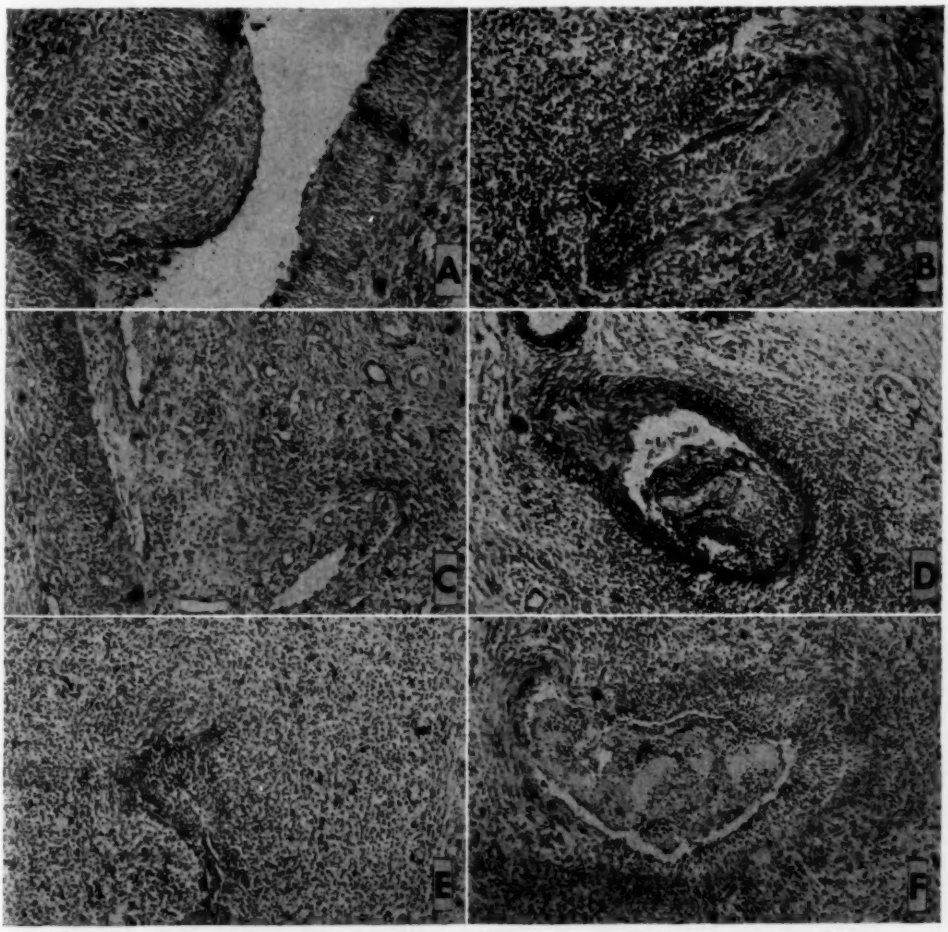


Fig. 1.—Mesenteric artery (*A*), testicular artery (*C*), and coronary arteries (*B, D, E, F*) showing characteristic inflammatory, necrotizing, and proliferative changes of periarteritis nodosa. (All sections stained with hematoxylin and eosin, ×100.)

DISCUSSION

In summary, a 4½-month-old infant is presented who died suddenly twenty-two days after the onset of what appeared to have been an ordinary upper respiratory infection. During his illness a variety of therapeutic agents was administered. The most noteworthy clinical phenomena during the three weeks of the terminal illness were the appearances of two skin eruptions, each following promptly upon the administration of oral penicillin. The second rash, blotchy and erythematous, was accompanied by typical urticaria. At autopsy widely disseminated periarteritis nodosa was disclosed with the coronary arteries being most seriously involved, and bilateral interstitial pneumonia.

Pathologically the case conforms to all the criteria laid down for the recognition and diagnosis of periarteritis nodosa. As has been pointed out by Miller and Daley,[20] the pathologic processes and appearances in periarteritis nodosa in childhood are similar to those seen in adults, save that they are less complicated by degenerative disease. The diagnosis must rest upon the demonstration of the characteristic and typical histopathologic lesions.[7] Of the four stages of the disease described by Arkin,[21] the first three, the alterative-degenerative, the acute inflammatory, and the granulation tissue stages are well represented. The healed end-stage was not seen, the disease having run a short fulminating course.

Of major interest in this case is the problem of etiology and the relation of the oral penicillin administration to the necrotizing arteritis. In the century which has elapsed since Rokitansky[22] first described the pathology, and in the eighty-five years since Kussmaul and Meier[23] first gave the disease its name and correlated the clinical course with gross and microscopic characteristics, the question of causation has been a moot point. Parasites, syphilis, viruses, hemolytic streptococci, and a specific infectious process[21] have all been cited as the offending agents, only to be ultimately discarded.[20] Relationship to the rheumatic group of diseases has been postulated.[24] Selye[25] states that periarteritis can be the consequence of exposure to a variety of nonspecific noxious agents. He demonstrated by animal experimentation that it was possible to produce a lesion indistinguishable from periarteritis nodosa by exposure to such a nonspecific factor as cold, and felt that it was "rather likely, therefore, that periarteritis nodosa belongs to the so-called diseases of adaptation."

In 1925 Gruber[26] declared that periarteritis nodosa was not a disease *sui generis* but that patients with this condition had an increased sensitivity of their arteries from a previous infection, and that the arterial lesions were the result of a hyperergic reaction to a variety of toxic and infectious processes. The past twenty-five years have seen the bulk of medical opinion and writing swing toward the side of allergy as the factor responsible for the spectacular vascular lesions. The experimental work of Rich and Gregory[27] and of Hopps and Wissler[28] and the clinical observations of Rich[29, 30, 31] and others[18, 19, 32] all have strengthened the position that hypersensitivity is the crux of the matter in the majority, if not in all cases of periarteritis nodosa. Although the precise relationships are not completely understood, experience has shown that there are widely different types of substances which have the potentiality of causing periarteritis nodosa in man.[19, 20, 29, 30, 33] The necessary adjuvant factors of constitutional and special tissue susceptibility cannot be predetermined clinically. Neale[17] suggested the presence of a specifically individualized arterial receptor mechanism for this type of allergic reaction.

During the decade from 1935 to 1945, the sulfonamides and horse serum were most frequently singled

out as the probable etiological agents. Recently cases of necrotizing arteritis attributed to penicillin have appeared. McCombs[34] has reported two cases in adults who developed periarteritis nodosa, proved by autopsy and biopsy, following the clinical appearance of untoward reactions to penicillin. Berne[35] has described necrotizing angiitis in a 53-year-old Italian storekeeper with pneumonia who was treated with penicillin in beeswax-peanut oil and sulfadiazine. He developed a rash following his *first* injection of the antibiotic, and the drug was discontinued. Following the disappearance of the rash, he was once more started on penicillin, and on the second occasion, he developed a severe bullous erythematous eruption which went on to generalized exfoliation, accompanied by asthma and hives. He died twenty-one days after the initiation of penicillin therapy and at autopsy disclosed severe inflammatory and destructive vascular disease with the coronary arteries showing the most profound changes.

The above course of events closely parallels the case reported here, including the appearance of a rash following the *first* administration of penicillin. While it cannot be categorically stated that the sensitivity in both cases was due to penicillin, nevertheless the history points to it as the most probable etiological agent. The sulfadiazine given in each case was small in amount and certainly in the child would not appear to have played an important part by itself. However, the possibility of its having acted synergistically with the penicillin cannot be eliminated.

If the reaction was due to penicillin, the question of the origin of the sensitivity presents itself. While the ability of penicillin to produce fatal anaphylaxis[36] and generalized exfoliative dermatitis[37] following previous sensitizing injections is known, neither the child here nor the adult in Berne's[35] case had ever received penicillin prior to his illness, and each reacted to the antibiotic in a hypersensitive fashion following the original administration. A possible explanation is furnished by the work of Gottschalk and Weiss[38] who stated on the basis of patch sensitivity tests carried out on several hundred volunteers that a small percentage of the population is *primarily* sensitive to penicillin and will react allergically on their first exposure, a phenomenon noted also by Rostenberg and Welch.[39] The possibility of in utero sensitization was postulated by Wilmer[13] in the case of a 10-day-old child who died with periarteritis nodosa and may account for some cases of primary sensitivity. The mother of the infant in the present case gave no history of past penicillin intake.

In postulating a hypersensitive state as the basis of periarteritis nodosa, no attempt is made to answer the question why, in a hypersensitive subject, the combination of antigen and antibody is damaging. This is all part of the larger problem of the mechanism of allergy itself, and histologic examination does not provide an answer as to why the damage is precisely and selectively localized in the arterial walls.[19] All that can be stated is the broad generalization that there is an individual constitutional difference in reactivity which determines not only the possibility of sensitization but also the character of the reaction and the tissue in which it will occur.

In closing it may be pointed out that the warning uttered by Rich[30] that "continued administration of a sulfonamide or of a foreign serum after symptoms of hypersensitivity have appeared carries the danger of producing visceral damage of the periarteritis nodosa type" applies equally to penicillin and must be kept in mind when allergic manifestations first make their appearance. Continued administration of a drug after symptoms of hypersensitivity have appeared is fraught with danger, and administration must be stopped before irreversible changes appear and irreparable damage has been done.

SUMMARY

A case of periarteritis nodosa in a 4½-month-old white male is reported. During his terminal illness which lasted twenty-two days, he was twice given penicillin by mouth and on each occasion reacted allergically. The probable relationship of the destructive arteritis to the penicillin hypersensitivity is pointed out.

The microphotographs were made by Mr. Lawrence Johnson, photographer to the Coroner of Cuyahoga County.

REFERENCES

1. Laipply, T. C.: Polyarteritis (Periarteritis) Nodosa, Review of Clinical and Anatomic Characteristics and Theories of Etiology, Am. Pract. 2: 795, 1948.
2. Heck, Frank J.: Introduction: Symposium on Periarteritis Nodosa, Proc. Staff Meet., Mayo Clin. 24: 17, 1949.
3. Logue, Bruce R., and Mullins, Frank: Polyarteritis Nodosa: Report of Eleven Cases With Review of Recent Literature, Ann. Int. Med. 24: 11, 1946.
4. Barnard, W. G., and Burbury, W. M.: Gangrene of the Fingers and Toes in a Case of Polyarteritis Nodosa, J. Path. & Bact. 39: 284, 1934.
5. Krahulik, Lambert, Rosenthal, Maurice, and Loughlin, Elmer H.: Periarteritis Nodosa (Necrotizing Panarteritis) in Childhood With Meningeal Involvement: Report of a Case With Study of Pathologic Findings, Am. J. M. Sc. 190: 309, 1935.
6. Keith, Haddow M., and Baggenstoss, Archie H.: Primary Arteritis (Periarteritis Nodosa) Among Children, J. PEDIAT. 18: 494, 1941.
7. Wold, Lester E., and Barker, Nelson W.: Periarteritis Nodosa (Essential Polyarteritis): Clinical Data on Thirty Cases Proved at Necropsy, Minnesota Med. 32: 715, 1949.
8. Rothstein, Jacob L., and Welt, Sara: Periarteritis Nodosa in Infancy and in Childhood: Report of Two Cases With Necropsy Observations; Abstracts of Cases in the Literature, Am. J. Dis. Child. 45: 1277, 1933.
9. Nowak, T. (Cited by Krahulik et al.): Case of Periarteritis Nodosa With Symptoms of Angina Pectoris in a Child Twelve Years Old, Polska gaz. lek. 12: 579, 1933.
10. Vining, C. Wilfred: A Case of Periarteritis Nodosa With Subcutaneous Lesions and Recovery, Arch. Dis. Child. 13: 31, 1938.
11. Coe, Meyeron, Reisman, Henry A., and DeHoff, John: Periarteritis Nodosa in a Nine-Year-Old Child, J. PEDIAT. 18: 793, 1941.
12. Scott, Edwin P., and Rotondo, C. C.: Periarteritis Nodosa: Report of Two Cases, One Complicated by Intrapericardial Hemorrhage, J. PEDIAT. 25: 306, 1944.
13. Wilmer, Harry A.: Two Cases of Periarteritis Nodosa Occurring in the First Month of Life, Bull. Johns Hopkins Hosp. 77: 275, 1945.
14. Bradley, Elizabeth J.: Periarteritis Nodosa in Childhood, J. PEDIAT. 31: 78, 1947.
15. Pickard, C. M., Owen, J. G., and Dammin, G. J.: Aneurysms of the Coronary Arteries Due to Polyarteritis Nodosa Occurring in an Infant: Report of a Case With Coronary Artery Thrombosis and Myocardial Infarction, J. Lab. & Clin. Med. 32: 1513, 1947.
16. Taylor, A. W., and Jacoby, N. M.: Acute Polyarteritis Nodosa in Childhood, Lancet 2: 792, 1949.
17. Neale, A. V.: Polyarteritis in Childhood, Arch. Dis. Child. 24: 224, 1949.
18. Kipkie, G. F., and Johnson, D. S.: Possible Pathogenic Mechanisms Responsible for Human Periarteritis Nodosa: As Suggested by the Occurrence of Two Instances of This Disease in Association With Glomerulonephritis, Arch. Path. 51: 387, 1951.
19. Hutchison, H. E.: Polyarteritis Nodosa: A Short Review, Glasgow M. J. 29: 116, 1948.
20. Miller, Henry G., and Daley, Raymond: Clinical Aspects of Polyarteritis Nodosa, Quart. J. Med. 15: 255, 1946.
21. Arkin, Aaron: A Clinical and Pathological Study of Periarteritis Nodosa: A Report of Five Cases, One Histologically Healed, Am. J. Path. 6: 401, 1930.
22. Von Rokitansky, C. (Cited by Laipply): Ueber einige der wichtigsten Erkrankungen der Arterien, Denkschr. d. k. Aknd. d. Wissensch. 4: 49, 1852.
23. Kussmaul, A., and Meier, R. (Cited by Wold and Barker): Ueber eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarteritis Nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht, Deutsches Arch. f. klin. Med. 1: 484, 1866.
24. Middleton, William S., and McCarter, John C.: The Diagnosis of Periarteritis Nodosa, Am. J. M. Sc. 190: 291, 1935.
25. Selye, Hans: The General Adaptation Syndrome and the Diseases of Adaptation, J. Clin. Endocrinol. 6: 117, 1946.
26. Gruber, G. B. (Cited by Rothstein and Welt): Virchows Arch. f. path. Anat. 258: 441, 1925.

27. Rich, Arnold R., and Gregory, John E.: The Experimental Demonstration That Periarteritis Nodosa Is a Manifestation of Hypersensitivity, Bull. Johns Hopkins Hosp. 72: 65, 1942.
28. Hopps, H. C., and Wissler, R. W.: The Experimental Production of Generalized Arteritis and Periarteritis (Periarteritis Nodosa), J. Lab. & Clin. Med. 31: 939, 1946.
29. Rich, Arnold R.: The Role of Hypersensitivity in Periarteritis Nodosa as Indicated by Seven Cases Developing During Serum Sickness and Sulfonamide Therapy, Bull. Johns Hopkins Hosp. 71: 123, 1942.
30. Rich, Arnold R.: Additional Evidence of the Role of Hypersensitivity in the Etiology of Periarteritis Nodosa: Another Case Associated With a Sulfonamide Reaction, Bull. Johns Hopkins Hosp. 71: 375, 1942.
31. Rich, Arnold R.: Hypersensitivity to Iodine as a Cause of Periarteritis Nodosa, Bull. Johns Hopkins Hosp. 77: 43, 1945.
32. Diaz-Rivera, R. S., and Miller, A. J.: Periarteritis Nodosa: A Clinicopathological Analysis of Seven Cases, Ann. Int. Med. 24: 420, 1946.
33. Van Wyk, Judson J., and Hoffmann, C. Rowell: Periarteritis Nodosa, a Case of Fatal Exfoliative Dermatitis Resulting From "Dilantin Sodium" Sensitization, Arch. Int. Med. 81: 605, 1948.
34. McCombs, Robert P.: Drug Allergies: Case Reports of Unusual Sequelae in Three Patients, Bull. New England Med. Center 13: 39, 1951.
35. Berne, Robert M.: An Unusual Sensitivity Reaction to Penicillin: Report of a Case With Autopsy Findings, New England J. Med. 242: 814, 1950.
36. Waldbott, George L.: Anaphylactic Death From Penicillin, J. A. M. A. 139: 526, 1949.
37. Rabinovitch, Jacob, and Snitkoff, Morris C.: Acute Exfoliative Dermatitis and Death Following Penicillin Therapy, J. A. M. A. 138: 496, 1948.
38. Gottschalk, Helen Reller, and Weiss, Richard S.: Epidermal Sensitivity to Penicillin, Arch. Dermat. & Syph. 53: 365, 1946.
39. Rostenberg, Adolph, Jr., and Welch, Henry: A Study of the Types of Hypersensitivity Induced by Penicillin, Am. J. M. Sc. 210: 157, 1945

STRAMONIUM POISONING

FRANK C. STILES, M.D.
MILWAUKEE, WIS.

STRAMONIUM poisoning in human beings may be produced by a plant whose botanical name is *Datura stramonium*. This plant is commonly called Jimson weed, Jamestown weed, apple of Peru, thorn apple, or devil's-apple. Because of the occasional occurrence of this type of poisoning in children, a case report and discussion are presented.

CASE REPORT

K. F., a 5-year-old white male, was admitted to Milwaukee Children's Hospital as a private patient. The boy seemed well until four hours prior to admission. After an afternoon of play, he came into the house and lay down on his bed, an unusual occurrence for this boy. He refused his supper and seemed "dopey and sleepy" to his parents. On arising from the bed, he stumbled and was unsteady of gait. The parents stated that the boy acted as if he were intoxicated. The child repeatedly looked behind a certain door in the room. His speech became garbled. He no longer recognized his parents, and kept moving his hands in the air as though he were trying to catch imaginary birds. No pain was evident, except that he stated his "tummy" hurt occasionally. This was disregarded, however, since the boy used such a complaint frequently to avoid eating. The child complained of a sour taste in his mouth after the ingestion of milk or water during the evening. His temperature was not elevated.

The past history revealed that one month prior to the present episode, the boy had been struck by a swing, and had sustained a contusion on the forehead, but had not lost consciousness. The parents felt that the child had developed a persecution complex since this incident. Past history revealed an apparently normal birth, growth, and development. No prior illnesses had occurred, and there was no history of operations or allergies. The family history was noncontributory.

Physical examination on admission showed a well-developed, very pale white child who exhibited extreme variations of mood. He was having visual hallucinations, but was not ataxic. Examination of the eyes revealed that the pupils were markedly dilated and did not react to light. Accommodation was poor. The extraocular movements seemed normal and no abnormality was noted when the fundi were visualized. A slight bilateral hyperactivity of the biceps and triceps reflexes was observed. Careful search revealed no other significant physical findings. The temperature was 99° F. rectally; the pulse was 80 beats per minute; the respiratory rate was 80 per minute; the blood pressure was 130/70.

Laboratory studies revealed a leucocyte count of 9,600 cells per cubic millimeter. The differential count showed 77 per cent segmented forms, 2 per cent monocytes, and 21 per cent lymphocytes. Slight toxic granulation of the polymorphonuclear leucocytes was noted, as was slight basophilic stippling of the erythrocytes. The hemoglobin was 12 Gm. per 100 c.c. The Mantoux test was negative; the Kline test was negative. X-rays of the skull revealed no abnormality. The long bones appeared normal.

The course of this patient during the first twenty-four hours was stormy. The boy was in a critical condition during this entire period. He remained afebrile. No history of ingestion of any poisonous substance had then been obtained. The boy was treated for acute poisoning of undetermined etiology. Because of the dilatation of

From the Department of Pediatrics, Marquette University School of Medicine, and Milwaukee Children's Hospital.

the pupils, the ingestion of an atropine-like substance was suspected. Gastric lavage was accomplished, using sterile water. The results were poor, however. A cathartic was administered; intravenous infusion with glucose in normal saline was supplied; sedation with a barbiturate was then found advisable. During the first twenty-four-hour period the child remained irrational. At the end of this time the boy showed rather sudden improvement. Within a few hours he became lucid and resumed normal activity; except for a slight dilatation of the pupils an apparently complete recovery was effected. The parents had made extensive investigations about the neighborhood for possible sources of poisoning. At this time, after the recovery was complete, a neighbor child reported that she had seen the patient "eating the seeds of a thorn apple" in a nearby vacant lot, just prior to the onset of the poisoning. The parents of the patient took a sample of this plant to the botanist at the Milwaukee Museum where it was identified as *D. stramonum*. When questioned, the patient admitted having eaten some seeds from this plant.

DISCUSSION

D. stramonium and other related species belong to the Solanaceae or nightshade family which includes such well-known plants as the red pepper, tobacco, tomato, belladonna, and bittersweet. The plant *D. stramonium* has a world-wide distribution, and grows wild in many areas of the United States, attaining a height of two to six feet. It flowers in the late spring and has a seed capsule which ripens in the early fall. The white, five-lobed, trumpet-shaped flowers have a strong, sweet scent. The seed capsules are egg-shaped and are covered with sharp spines. The leaves are large, angular, and measure from four to six inches in length. All parts of the plant are poisonous, containing the alkaloids atropine, scopolamine, and hyoscyamine. The term "thorn apple" is inappropriately used to describe *D. stramonium*, since this term is used as a name for the fruit of the hawthorn bush.

Poisoning is caused by ingestion of any part of the plant, but especially the seeds and the fruit. One case was reported from the inhalation of pollen from a full-blown flower.[9] A number of cases of poisoning have resulted from the mistaken use of this plant in making senna tea and as a treatment for asthma. Smoking of this weed may produce daturism. *D. stramonium* has occasionally been planted on farms supposedly to prevent hog cholera.

Jennings[6] notes that in the *Iliad*, in *Romeo and Juliet*, and in *Antony and Cleopatra*, instances are mentioned which lead us to believe that the ancients were familiar with the hypnotic and narcotic effects of the Datura species. In India, a species of Datura is said to have been used for many decades by thugs for the purpose of drugging their victims. In such cases the seeds were combined with tobacco, sugar, or flour. Evidence of early use among the Hindus is shown by a report of twenty-one fatalities by a medical journal from India in 1676. Probably the first report in this country, according to Hughes and Clark,[4] was that described by Robert Beverly in Virginia in 1676. Interestingly enough, the name "Jamestown weed" dates back to this same year, when Captain John Smith was sent with a group of men to quell a rebellion in Jamestown, Va. Sporadic cases have appeared in the literature since then. Taylor[9] states that in 1864 Turner reported five cases in children under 10 years of age. In 1915 Ismael[5] reported that in Egypt, Datura poisoning "ranks second in frequency to acute alcoholic intoxication among those brought to the hospital in an unconscious state." In 1923 an outbreak of thirty cases in an orphanage was described.[4]

A number of fatalities from daturism have been reported. One case terminated in six hours.[9] A death from smoking the seeds was recorded

in 1937 by Henke.[9] The amounts necessary to produce a fatality have varied. Brundage[1] reports a death in a 2-year-old-child from the ingestion of 100 seeds of stramonium, and a recovery after taking one-half ounce of leaves infused in boiling water.

The symptoms of stramonium poisoning are varied. However, premonitory sensations of abnormal thirst and visual difficulties are almost always present. Other signs include feelings of intoxication, euphoria, irritability, restlessness, and fear. Convulsions and opisthotonos have been described. The patient may become maniacal and totally unmanageable. I am struck by the frequency with which patients have been described as "picking at imaginary objects," as did the patient in the case here presented.

Physical examination characteristically reveals that the pupils of the patient are dilated. Dryness of the oral mucous membranes is common. The skin may be hot, dry, and flushed. Thus there may be a diffuse erythema resembling scarlet fever. Tachycardia is almost invariably present. One observer, Ismael,[5] states that the rapidity of the pulse is the best index to the degree of intoxication. Fever may or may not be present, but is usually absent.

The diagnosis may be made on the history, recovery of portions of the plant, or identification of the alkaloids from the gastric washings, and on the clinical findings. It must be remembered that similar symptoms may be produced by other plants of the Datura group including angel's-trumpet or *Datura metaloides* (containing alkaloids similar to stramonium), "deadly nightshade" (belladonna), Jerusalem cherry, or poison hemlock (coniine). The latter is often used by schoolboys to make whistles.

The prognosis is usually good, as most patients recover in one to two days, although mydriasis may persist for one week or more. Sequelae are uncommon. Fatalities, as has been emphasized, may occur.

Treatment if given early, may be effective. Hughes and Clark[4] emphasize the importance of gastric lavage with 4 per cent tannic acid, in order to precipitate the alkaloids. Emetics and catharties are also advised. Sedation is usually necessary. Morphine is contraindicated because of its known synergistic action with atropine and scopolamine, and its tendency to produce cerebral congestion. Warm packs may aid in relaxing the patient and may hasten drug excretion by promoting diaphoresis.

SUMMARY

1. A case of stramonium poisoning with recovery in a 5-year-old boy is presented.

2. The plant *D. stramonium* (Jimson weed, Jamestown weed) is described briefly.

3. Historical notes of interest are presented.

4. The signs, symptoms, treatment, and prognosis of stramonium poisoning are discussed.

Appreciation is expressed to Dr. E. Epstein and Dr. D. Zubatsky for permission to present this patient who was under their private care.

REFERENCES

1. Brundage, A. H.: Manual of Toxicology, New York, 1929, D. Appleton-Century Co., p. 537.
2. Garvin, J. A., and Rush, H. O.: Acute Poisoning Due to Eating the Seeds of the Jimson Weed (Datura Stramonium). Arch. Pediat. 40: 827, 1923.
3. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, 1941, The Macmillan Co., pp. 460-477.
4. Hughes, J. D., and Clark, J. A.: Stramonium Poisoning. A Report of Two Cases, J. A. M. A. 112: 2500, 1939.
5. Ismael, A.: Poisoning by Datura and Hyoscyamus, Practitioner 94: 121, 1915.
6. Jennings, R. E.: Stramonium Poisoning. Review of the Literature and Report of Two Cases, J. PEDIAT. 6: 657, 1935.
7. McNally, W. D.: A Case of Stramonium Poisoning, J. A. M. A. 65: 1640, 1915.
8. Reese, J. J., and Leffman, H.: Textbook of Medical Jurisprudence and Toxicology, Philadelphia, 1903, P. Blakiston's Son & Co., p. 608.
9. Taylor, A. S.: A Treatise on Poisons, Philadelphia, 1875, Henry C. Lea Co., pp. 736-743.

PERFORATION OF THE STOMACH IN THE NEWBORN INFANT

A Report of a Survival

Lieutenant (jg) Huston G. Kellogg (MC), USNR, Commander Sol M. Abelson (MC), USN, and Lieutenant Forest A. Cornwell (MC), USNR

VERY few cases of perforation of the stomach of the newborn infant have been reported. Two complete reviews of gastrointestinal tract perforations have been published in recent years.[1, 2] Since 1941 only four cases of perforated gastric ulcers in the newborn infant have appeared in the world's literature of which none have survived.

CASE PRESENTATION

B. B. B., a newborn white male was delivered on the obstetrical service of the U. S. Naval Hospital, San Diego, Calif., on March 23, 1951, weighing 5 pounds, 13 ounces. The mother was an 18-year-old white Latin American married to a 19-year-old white male. The mother was gravida i, para 0, who had an uneventful prenatal course. The serology of the mother was negative and both father and mother were Rh positive. The infant was delivered spontaneously under analgesia consisting of 100 mg. of Demerol hydrochloride and 1/100 gr. of scopolamine hydrobromide. The length of the first stage of labor was fourteen hours while the second stage lasted fifty minutes. The infant's condition was good at birth, the cry was vigorous, and no resuscitation, suction, or respiratory stimulants were used. Respirations were established in one-half minute, were normal in one minute, and no oxygen was necessary in the delivery room. About twelve hours after birth the infant became quite cyanotic and was placed in continuous oxygen. No cardiac murmur was heard but auscultation suggested poor expansion of the left lung. An x-ray of the chest taken at this time, however, showed no gross evidence of atelectasis. The film of the chest also included the abdomen and no abnormalities were noted (Fig. 1). Antibiotics in the form of streptomycin, 1/16 Gm. every six hours, and penicillin, 100,000 units every six hours, were administered.

On March 24, the first day of life, the infant had normal meconium and was urinating normally. The first feeding was on this date and consisted of breast feedings and water. After the infant was placed in oxygen, formula feedings were given in the amounts of one to two ounces every three hours by bottle. On the third day the infant had improved. The stomach was aspirated and gavaged several times and the stools became yellow. He regurgitated once. There was no gross blood in either the stools or vomitus. The weight at this time was 5 pounds, 9 ounces. At 2 A.M. on March 27, the fourth day of life, the baby became acutely worse as manifested by an ashen gray pallor and listlessness. Examination of the abdomen at that time revealed nothing remarkable. At 9 A.M. the baby's general condition had not improved and there was moderate abdominal distention with tenderness and dullness to percussion in the lower third and tympany in the upper two-thirds. The white blood count was 10,500 with 70 per cent neutrophiles and 30 per cent lymphocytes. The red cell count was

From the pediatric service of the U. S. Naval Hospital, San Diego, Calif.

The opinions or assertations contained in this article are the private ones of the writers and are not to be construed to be official or reflect the views of the Navy Department or naval service at large.

4,200,000 with 13 Gm. of hemoglobin. The rectal temperature was normal. An x-ray of the abdomen including the chest showed a "massive pneumoperitoneum and evidence of a fluid level in the mid-abdomen, suggesting some peritoneal fluid. The lungs were essentially clear." (Fig. 2.) Clinically it was felt that the infant had findings indicative of a perforated abdominal viscus.

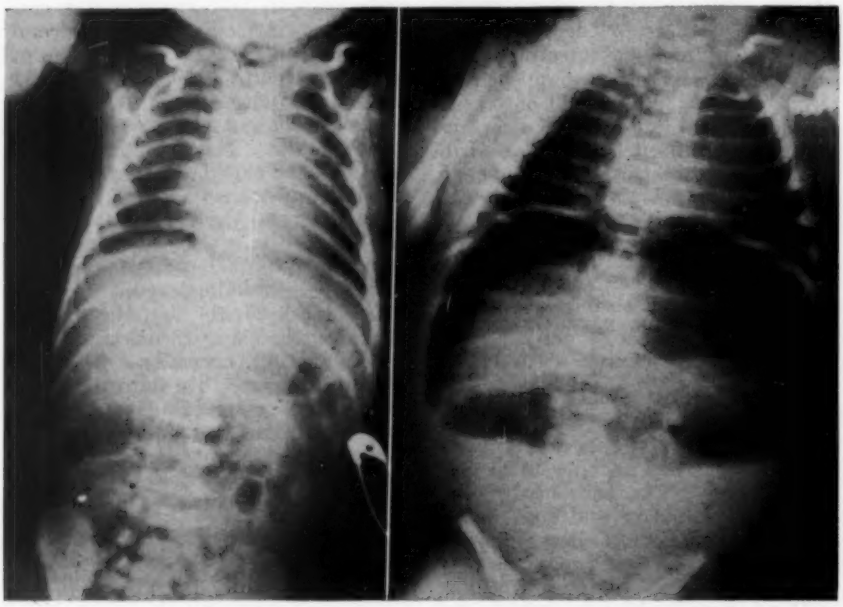


Fig. 1. Fig. 2.

Fig. 1.—X-ray soon after birth.
Fig. 2.—X-ray at 4 days of age, showing a massive pneumoperitoneum.

Laparotomy by Commander B. W. Clark (MC), USN was performed at 4 days of age, about twelve hours after the acute turn for the worse, under general anesthetic of ether, cyclopropane, and nitrous oxide. As the peritoneum was opened, air escaped under pressure, and a yellow cystic mass presented itself in the wound. This exuded a thick creamy substance with the consistency and appearance of pus. A biopsy was taken from the cystic mass and a sample of the purulent material was taken. Upon exploration it was found that the yellow cystic mass was omentum containing a cyst with necrosis, involving the entire omentum which had a yellowish appearance. All free fluid and this thick creamy substance were evacuated from the abdominal cavity. Exploration revealed normal liver, gall bladder, biliary tract, anterior wall of the stomach, duodenum, and the small bowel was normal except for a Meckel's diverticulum with a small adhesive band from the diverticulum down to the mesentery. This fibrous band was separated, freeing the diverticulum from this attachment. The ileocecal area, the large bowel, and the appendix were normal. Returning to the upper abdomen, the posterior wall of the stomach was investigated and on the posterior

superior surface, just distal to the cardia and at the greater curvature, a perforated ulcer was found which measured about 2½ by 2 cm. This was closed with a double row of 5-0 chromic catgut in a continuous suture. All free fluid was aspirated from the abdominal cavity. All bleeding having been controlled, the abdomen was closed in layers using 4-0 chromic suture on the peritoneum and No. 60 cotton suture on the anterior fascia and skin. No drains were inserted. During the surgical procedure 70 c.c. of whole blood were administered through a polyethylene tube which was inserted into the anterior medial malleolus vein on the right. The postoperative course immediately after surgery was fair and the infant was returned to the pediatric ward with the polyethylene tubing still in place and with blood still being received.

Tissue examination by the pathologist revealed the biopsy of the cystic mass taken to be a "flat epithelial-lined cyst wall with a purulent exudate on the surface. There was no evidence of malignancy." Culture of the purulent material from the abdominal cavity revealed *Escherichia coli* and gram-negative bacteria, biochemically, *Alcaligenes fecalis*.

Postoperatively the infant was placed in continuous oxygen in a

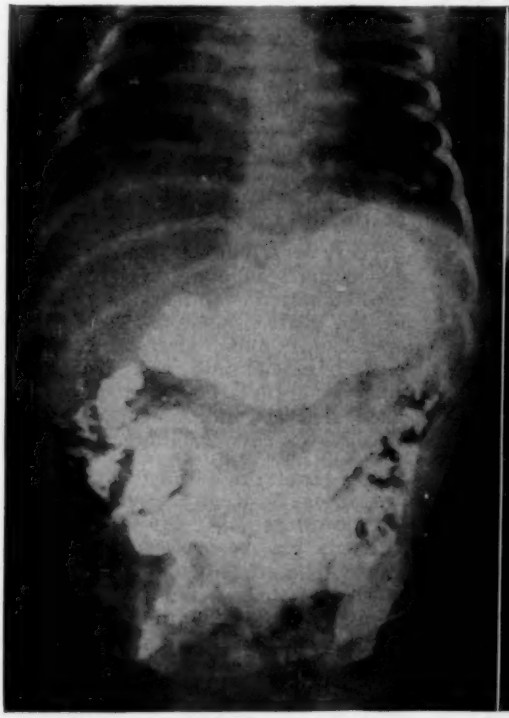


Fig. 3.

Fig. 4.

Fig. 3.—X-ray at 44 days of age, thirty minutes after oral administration of barium, showing no obstruction or other abnormality.

Fig. 4.—Granulating abdominal wound on discharge at 45 days of age.

Gordon-Armstrong incubator. Nothing was given by mouth for two days and nutrition was maintained by intravenous feedings through the polyethylene "cutdown" and consisted of dextrose-Amigen-Ringer's lactate solution along with glucose in water and also in saline. Streptomycin in a dosage of ⅛ Gm. every six hours, and aqueous penicillin, 50,000 units every three hours, were administered. One hundred milligrams of ascorbic acid daily 2 c.c. of parenteral multivitamins every other day, and ½ c.c. of crude liver extract intramuscularly every other day were also given. Wangensteen suction was continued for four days.

On the day following surgery the temperature reached 102° F. rectally, but the infant clinically looked good. The second postoperative day he had a small yellow bowel movement. On March 29, the second postoperative day, small one to two ounce feedings of glucose in water were given orally, the Wangensteen gastric suction being clamped off two hours prior to feeding and one hour post-feeding. On March 30, the third postoperative day, the Wangensteen was clamped off and a formula containing one part of evaporated milk to one part of water was given in the amount of two ounces every three hours. This was gradually increased to three ounces every three hours after several days. The intravenous cutdown and the Wangensteen gastric suction were both discontinued on March 31, four days postoperatively. On April 2 the dosage of streptomycin was decreased to $\frac{1}{16}$ Gm. every six hours, and the penicillin dosage reduced to 50,000 units every six hours intramuscularly. The streptomycin was discontinued on April 7 and 50 mg. of aureomycin given by mouth every six hours instead.

The infant remained afebrile after April 4, but gained weight very slowly, weighing only 5 pounds, 9½ ounces by April 6. It was decided, therefore, to give a 50 c.c. clysis of 2½ per cent glucose in distilled water every eight hours and this was continued for four days; then only one 50 c.c. clysis was given daily. The infant was removed from oxygen therapy on April 10, the fourteenth postoperative day.

At the age of 17 days, or thirteen days postoperatively, periodic postfeeding crying developed which responded dramatically to the administration of Amphojel in a dosage of ½ dram given between feedings, suggesting the presence of a peptic ulcer or colic. However, on May 7, forty-one days postoperatively, films of the gastrointestinal tract following ingestion of barium showed "no gross abnormalities and the stomach emptied well." (Fig. 3.)

There was delayed healing of the abdominal wound apparently due to a combination of infection, irritation by the gastric juices at the time of operation, and marasmus. The patient gained and was discharged with a granulating wound but in good general condition on May 8, at 45 days of age, weighing 6 pounds, 12½ ounces. (Fig. 4.)

DISCUSSION

There has been a great deal of study done on the etiology of gastric ulcer in human beings. When they occur in newborn infants, speculations reach new heights. Many conditions have been suspected as etiological agents. Guthrie[3] discusses several: circulatory disturbance leading to ischemia and ulceration, direct trauma to the mucous membranes, sepsis, burns, marasmic conditions, and external violence. Morganti[4] reports two cases of gastric ulcer associated with cerebral hemorrhage. Crawford and Stewart[5] report a case complicating erythroblastosis fetalis. Several cases have been associated with obstruction of the gastrointestinal system (e.g., Burdick[6]) and congenital anomalies (Bastman[7]). Miller[8] has observed that gastric acidity reaches a height

comparable to that of adults at 48 hours of life, and this may play a part in autolysis of the mucous membranes. The etiology of our patient is obscure. It seems unlikely that sepsis was the cause as the gastric ulceration progressed in spite of intensive antibiotic therapy. However, since our patient was aspirated and gavaged several times before perforation occurred, the possibility of mechanical trauma as an etiological factor cannot be ruled out.

There have been very few cases of perforation of the stomach of the newborn infant reported. Thelander[1] cited as the first case that reported by Siebold in 1825. Tow[9] in 1938 reported a case which he felt was the fourteenth in the world's literature. Bird, Limper, and Mayer[2] in a complete review of the literature in 1941 were able to find only five cases of perforated gastric and duodenal ulcers in the first fourteen days of life, which had been surgically repaired. Their personal case, a 34½-hour-old infant with a duodenal perforation, was the only survival. So far as we have been able to determine in a review of the world's literature there have been only four perforated gastric ulcers in the newborn infant reported since 1941.

Quinn[10] reported two cases which perforated on the second and fifth days. One was repaired but the infant died on the fifth day post-operatively of bronchopneumonia. Wright and Scott[11] reported one case which was diagnosed on the fifth day of life, but the baby expired before surgery could be accomplished. Bianchi and Zanardi[12] reported a case of an infant with multiple gastric ulcers and peritonitis who was not operated upon and died on the fifth day of life. Our patient has the distinction of being the second case of perforated gastric ulcer in the newborn infant ever operated upon and the only survival ever reported in the world's literature.

We wish to emphasize the importance of early antibiotic therapy where a diagnosis of an obscure but obviously serious condition presents itself in the newborn period. The use of penicillin and streptomycin soon after birth, before the diagnosis was established, gave the baby a distinct advantage. In this connection Thelander[1] in 1939 first treated such a case with sulfanilamide and emphasized the importance of combating infection.

Some cases reported might lead the reader to think that a perforation is congenital. Lee and Wells[13] reported a case which perforated in utero, and Ladd and Gross[14] reported it in a stillborn. Although our patient had cyanosis, listlessness, vomiting, and occasional irritability (however no melena) in the first few days, which are recorded ulcer symptoms in the newborn period, a perforation was not present, because there is x-ray proof (Fig. 1). This case reaffirms the value of an abdominal x-ray as a diagnostic aid in the newborn infant, as has been pointed out recently by Krafft, Neal, and Henderson.[15]

SUMMARY

1. A rare case and the only known survival of a perforated gastric ulcer in the newborn period is presented.

2. Early diagnosis, early use of antibiotics, and early surgical repair made survival possible.

3. Serial x-rays are presented which show that the perforation was not congenital.

REFERENCES

1. Thelander, H. E., and Mathes, M.: Duodenal Perforation in a Newborn Infant, Treated Surgically and With Sulfanilamide, Am. J. Dis. Child. 57: 596, 1939.
2. Bird, C. E., Limper, M. A., and Mayer, J. M.: Surgery in Peptic Ulceration of Stomach and Duodenum in Infants and Children, Ann. Surg. 114: 526, 1941.
3. Guthrie, K.: Peptic Ulcer in Infancy and Childhood With Review of Literature, Arch. Dis. Childhood 17: 82, 1942.
4. Morganti, F.: Gastric Ulcer in Newborn; Possible Etiologic Significance of Cerebral Hemorrhage, Pediatria 48: 764, 1940.

5. Crawford, R., and Stewart, C. A.: Gastric Ulceration Complicating Erythroblastosis Fetalis, Journal-Lancet **63**: 131, 1943.
6. Burdick, W. F.: Peptic Ulcer in Children; Report of Ten Cases, J. PEDIAT. **17**: 654, 1940.
7. Bastman, L.: Perforated Gastric Ulcer With Melena Due to Torsion of Stomach and Diaphragmatic Anomaly in Newborn, Acta paediat. **28**: 314, 1941.
8. Miller, R. A.: Observations on Gastric Acidity During First Month of Life, Arch. Dis. Childhood **16**: 22, 1941.
9. Tow, A., and Ross, H.: Rupture of Stomach in Newborn, J. A. M. A. **111**: 1178, 1938.
10. Quinn, A. G.: Report of Two Ruptured Gastric Ulcers and One Ruptured Duodenal Ulcer in Three Newborn Infants, South. M. J. **33**: 1171, 1940.
11. Wright, L. T., and Scott, B. E.: Perforated Gastric Ulcer in a Newborn Infant, J. PEDIAT. **37**: 905, 1950.
12. Bianchi, P. G., and Zanardi, S.: Gastric Ulcers in Newborn; Five Cases, Minerva Pediat. **1**: 264, 1949.
13. Lee, W. E., and Wells, J. R.: Perforation in Utero of a Gastric Ulcer, Ann. Surg. **78**: 36, 1923.
14. Ladd, W. E., and Gross, R. E.: Abdominal Surgery of Infancy and Childhood, Philadelphia and London, 1941, W. B. Saunders Co., p. 19.
15. Krafft, C. J., Neal, R. F., and Henderson, A. T.: Congenital Duodenal Obstruction **39**: 44, 1951.

Medical Progress

PEDIATRIC ASPECTS OF CEREBRAL PALSY

ERIC DENHOFF, M.D., AND RAYMOND H. HOLDEN, M.A.
PROVIDENCE, R. I.

INTRODUCTION

THE pediatrician's role with cerebral palsied children and their parents is a diverse and difficult one. It is his responsibility to diagnose cerebral palsy early, to investigate the need for surgical intervention, and to alleviate the many disturbing manifestations peculiar to these brain-damaged children. As the youngster grows, the pediatrician must constantly evaluate the physical, mental, and emotional status, and formulate a general working plan for the future. This is essential since he is the one parents confront with questions regarding the prognosis of motor and mental development, plans for the training and education, and, finally, home versus institutional care. Above all it is the pediatrician's responsibility to discuss with parents their misfortune in a manner that will maintain their confidence, so that he can properly guide them through the devious pathways parents must take before and after the answer to their particular problem is clarified.

If pediatricians are to fulfill their role, they will be especially in need of simple, specific criteria to help them achieve a practical positive treatment approach.

The primary reason for this paper is to demonstrate how the material gathered in a cerebral palsy center can be utilized by the pediatrician or general practitioner in routine office practice to help parents. In addition, since the failure to diagnose or treat properly the cerebral palsied child is a constant worry to the physician who sees his patients at regular intervals during early life, perhaps this report may help clarify that phase of his practice.

Presented to the American Academy of Cerebral Palsy, Chicago, Ill., Oct. 20, 1950.

MATERIAL AND METHODS

The patients studied were selected from the Meeting Street School for Cerebral Palsied Children in Providence, R. I.,[1] and the Emma Pendleton Bradley Home, a children's neuropsychiatric hospital that formerly had a cerebral palsy service. The controls utilized were 504 mothers and their infants born at the Providence, Rhode Island, Lying-In Hospital during 1949. These were considered normal infants after a two-year follow-up. Standards for normal and late normal developmental items are those of Gesell and Amatruda.[2] The statistical data presented are significant above the 1 per cent level.

DIAGNOSIS

Hints From History.—Whether the pediatrician sees the patient at birth or in later years, there are certain essentials in the history which support a diagnosis of cerebral palsy. A positive history of maternal pregnancy disorders, obstetrical complications, pre-

maturity, oxygen need at birth, neonatal or infancy illness, or slow developmental progress, alone or in combinations, indicate possible brain damage. The following data form the basis for this opinion.

Maternal Pregnancy Disorders.—Seventy per cent of 100 mothers of cerebral palsied children reported a wide variety of diseases, illnesses, or unusual conditions during the pregnancy of their cerebral palsied offspring. There were no chronic conditions considered significant, but of the acute conditions reported later than the first trimester, nausea and vomiting, hypertension, anemia, and vaginal hemorrhages showed differences which were statistically significant when compared with the control group. Twenty-eight per cent of these mothers reported previous incomplete pregnancies. This is a highly significant statistical difference from mothers studied on a large obstetrical service.[3]

Obstetrical History.—Sixty per cent of the 100 mothers had complications associated with delivery. Those which showed a significant difference from the control group were mid-forceps and breech delivery. Prolonged pregnancy or labor, precipitate delivery, high for-

TABLE I. SIGNIFICANT FACTORS IN HISTORIES OF 100 CEREBRAL PALSIED CHILDREN

	NUMBER AND PER CENT	SIGNIFICANT FACTORS*	NUMBER AND PER CENT†	FACTORS NOT SIGNIFICANT	NUMBER AND PER CENT	FACTORS NOT FOUND IN CONTROLS	NUMBER AND PER CENT
Maternal pregnancy disorders	70	Nausea & vomiting	23	Toxemia	4	Phlebitis	4
		Hypertension	14	Pelvic inflammatory disease	2	Hypothyroidism	4
		Anemia	12	Nephritis	1	Accidents to abdomen	3
		Vaginal hemorrhage	12	Diabetes	1	Hepatitis	3
	28	Incomplete pregnancies	28			Miscellaneous	9
Obstetrical complications	60	Mid-forceps delivery	16	Low forceps delivery	11	Prolonged labor	10
		Breech delivery	9	Cesarean delivery	5	Prolonged pregnancy	7
				Maternal age		Precipitate delivery	5
						High forceps delivery	5
						Premature rupture	4
						Miscellanous	2
Birth-neonatal complications	67	Oxygen required and/or transfusions	37	Vomiting	3	Convulsions	10
		Prematurity	30	Asphyxia from cord	1		
Illness during infancy	50	Convulsions, cause undetermined	23				
		Hemorrhagic disease	23				
		Infectious disease	4				

*Significant—1 per cent level confidence when computed against 504 controls.
†Based on 100 cases; number of cerebral palsied also equals per cent cerebral palsies.

ceps delivery, and premature rupture were also reported, while none of these was found in the control group.

Patient History.—

Birth-Neonatal: Of the 100 cerebral palsied children studied, 37 per cent required oxygen and/or transfusions at birth, while 30 per cent were premature. Of this group, only 18 per cent received oxygen. Ten per cent of the entire group had convulsions during the neonatal period.

Infancy: Fifty per cent of the patients had some serious illness after the neonatal period (after 2 weeks of age) but prior to the recognized onset of cerebral palsy. Convulsions of unknown etiology and hemorrhagic diseases of the newborn were outstanding. Because of recency of routine testing, Rh studies are incomplete. (Table I.)

Developmental History.—In retrospect, parents reported developmental retardation in the form of inability to lift head from the prone position by 3 months of age in 68 per cent of the cases. By the end of the first 1½ years, most of the children failed to achieve maturity in several developmental items.

From a diagnostic viewpoint, failure to maintain the developmental schedule, with an ever-widening gap in the ages of sitting, standing, walking, and talking are among the outstanding characteristics of cerebral palsy.

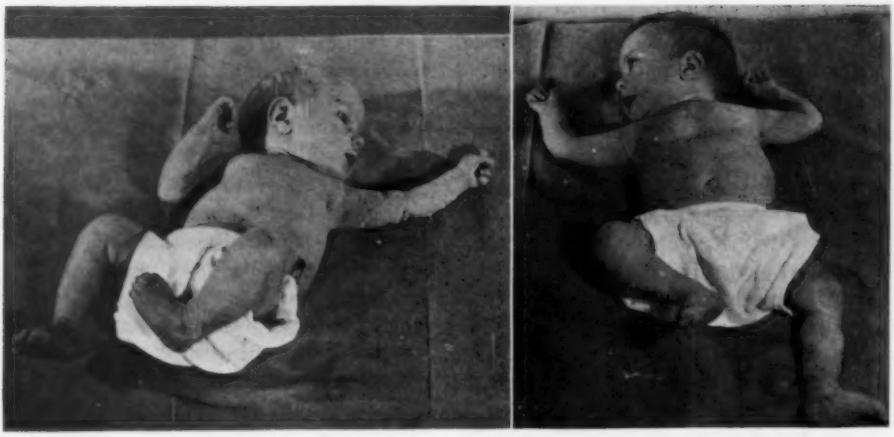
Birth-Neonatal: At birth or during the neonatal period moderate or severe brain damage may be reflected by a multitude of signs such as cyanosis or pallor, hypertonicity or listlessness, twitchings or convulsions, or feeding difficulties of a generalized nature. In minimal cases, the inability of the neonate to resist a slow pull upward from the supine to sitting position, may be an important early sign, since infants who fall into this group later have been found to have a higher incidence of neuropathologic conditions than those whose heads lift up and whose bodies resist strongly the pull upwards.[4]

Infancy: During infancy, slow development may be the only unusual finding. During the early months, poor head control or neck tonus associated with refusal to nurse, difficult sucking or swallowing, excess crying, vomiting or grunting, or other signs in excess, must be regarded with suspicion.

As the infant grows, deviations from the normal developmental schedules must be regarded seriously. The presence of fisted hands after 4 months, the persistence of the tonic neck reflex after 6 months, inability to sit without support, crawl, grasp, stand, walk, or talk within normal levels frequently are indicative of later neuromotor dysfunction (Figs. 1 to 6). A progress record for office use has been found helpful in evaluating developmental progress and aiding in an early diagnosis of brain damage when it is present (Chart I).

Preschool Child.—Between the second and third year of life, suggestive abnormal neuromotor patterns become stabilized, and, depending upon the degree of damage, classical criteria of cerebral palsy become obvious. There is no need to describe the findings which characterize a severe or moderate case of spasticity or athetosis, since these are well described in standard texts.[17, 18]

It is the mildly palsied child that frequently presents a problem in diagnosis. Strauss' neurological screening examination has been found useful in these cases. A normal examination is fairly definite evidence that the child

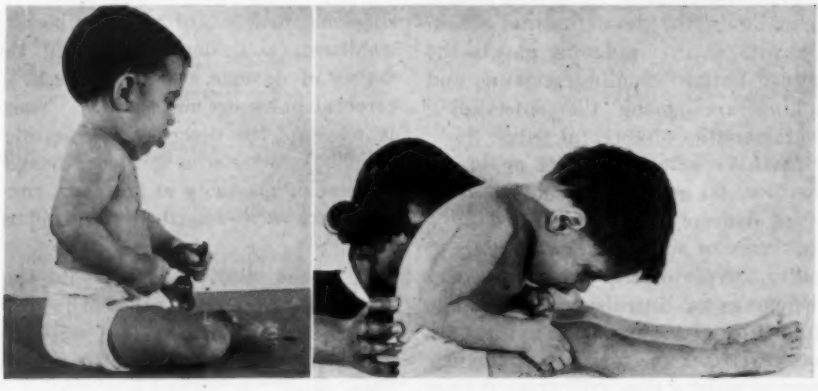


A. *B.*

Fig. 1.—Tonic neck reflex. *A*, Normal, 6 weeks. *B*, Cerebral palsy, 7 months.

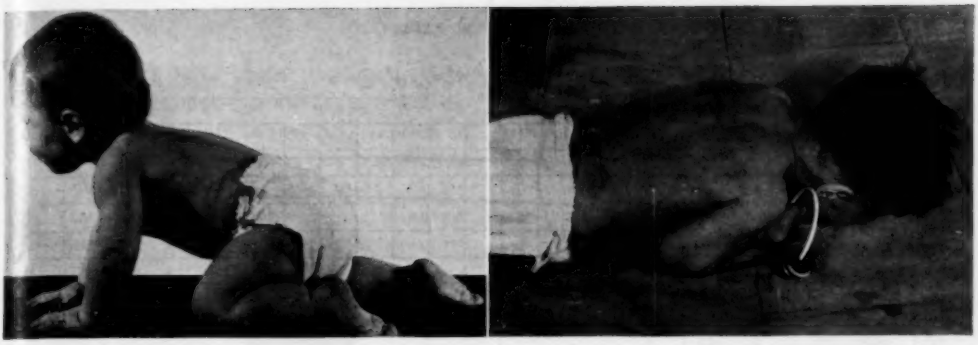
A. *B.*

Fig. 2.—Head control. *A*, Normal, 3 months. *B*, Cerebral palsy, 7 months.



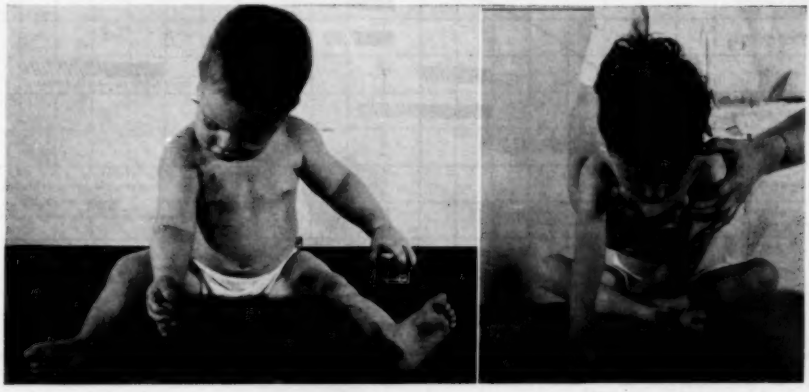
A. *B.*

Fig. 3.—Sitting. *A*, Normal, 6 months. *B*, Cerebral palsy, 2 years.



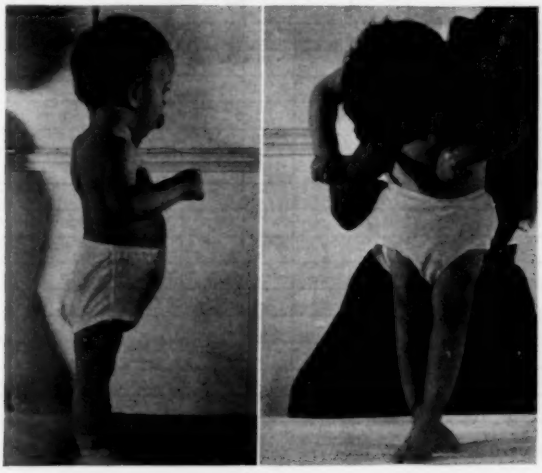
A. *B.*

Fig. 4.—Crawling. *A*, Normal, 9 months. *B*, Cerebral palsy, 2 years.



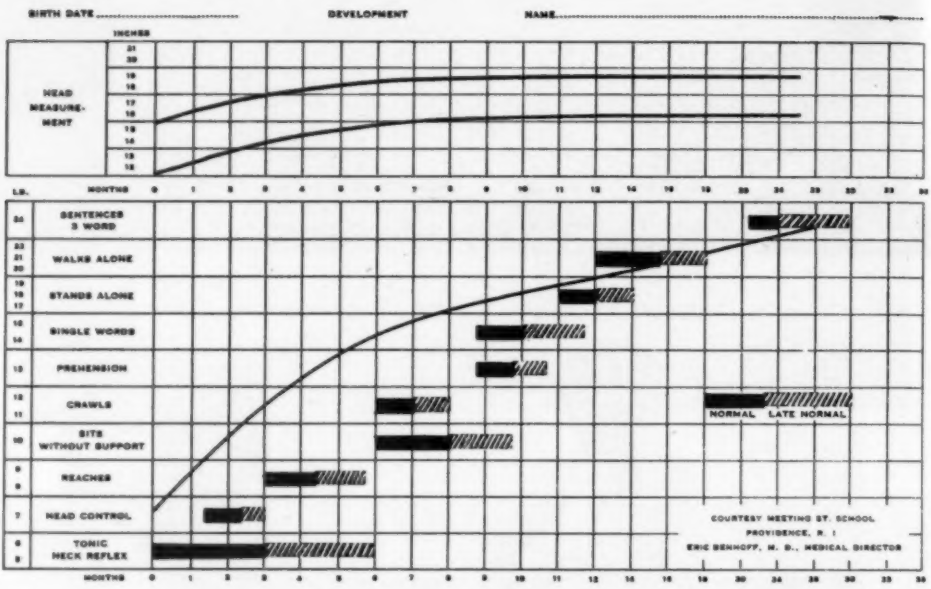
A. *B.*

Fig. 5.—Prehensile grasp. *A*, Normal, 10 months. *B*, Cerebral palsy, 2 years.



A. *B.*

Fig. 6.—Standing. *A*, Normal, 12 months. *B*, Cerebral palsy, 2 years.



NAME.....

MEASUREMENTS					FEEDING						HISTORY (RECORD NUMBERS OF FOLLOWING SYMPTOMS, IF POSITIVE)
DATE	WT.	HT.	HEAD	CHEST	MILK	DEXTRI-MALTOSE	WATER	VITAMINS	APPETITE	STOOLS	(1) REFUSAL TO NURSE (2) DIFFICULT SUCKING (3) DIFFICULT SWALLOW (4) EXCESS CRYING (5) VOMITING (6) HYPERIRRITABLE (7) FEEBLE CRY (8) EXCESS DROWSINESS (9) LISTLESS (10) EXCESS GRUNTING (11) IRREGULAR RESPIRATION (12) CYANOSIS (13) PALLOR (14) STIFFENING (15) ARCHING (16) STARTLE (17) STRABISMUS (18) TWITCHING (19) CONVULSIONS (20) BRUISES (21) HEMORRHAGE (22) JAUNDICE.

IMMUNIZATIONS			
DATE	TYPE	BRAND	DOSE

Chart I.—Monthly progress chart for use in office practice.

does not have brain damage.[5] However, minimal variations in deep reflexes and tonus, abnormal reaction of certain cranial nerves, the presence of pathologic reflexes, and slight abnormalities in movement and coordination are frequently indicative of cerebral palsy (Chart II).

Behavior.—A series of studies by Bradley and his associates have carefully delineated a characteristic type of behavior consistently related to the presence of organic cerebral damage prior to early childhood. This behavior may be manifested by hyperactivity, irritability, impulsiveness, dis-

NORMAL REFLEXES (Frequently Abnormal in Cerebral Palsy)	PATHOLOGIC REFLEXES (Frequently Present in Cerebral Palsy)
CRANIAL NERVES	
Pupils	
N III, IV, VI	
N VII	
N XII	Nystagmus
DEEP REFLEXES	MOVEMENT: Adiadokokinesis, Athetosis, Chorea
Biceps	
Radial	GAIT: Spastic, Ataxic, Cerebellar
Abdominal	
	TONUS: Hypertonic, Plastic, Rigid
Patellar	Stretch
	Oppenheim
Ankle	Babinski

Significant Even if Solitary	Significant When 2 or More Are Present
Babinski: 0–2 years Normal; 2–10 years Slow Development or Brain Injury	Pupils: Light reflex sluggish or absent
Paralysis of: N III) IV) VI) Strabismus	Nystagmus: Especially when unilateral
N VII Facial Paralysis	Oppenheim's Sign:
N XII Tongue Deviation	Adiadokokinesis:
	Babinski, modified
	Increasing or decreasing deep reflexes — Especially when unilateral

Chart II.—Scheme for short neurological examination to determine presence of brain injury.

tractability, or short attention span.[6] There are some children whose primary difficulty may be behavioral but if they are found to have minimal neurological variations as described by Strauss, these children, too, should be regarded as cerebral palsied.

Psychological Evaluation.—The destiny of a cerebral palsied child depends not only on physical improvement but also on the mental and emotional status. The pediatrician has available several leads to proper psychological evaluation from information obtained from the history, physical and developmental examinations, from psychological tests, and from behavioral observations in a group or at home.

A cerebral palsied child with a history of familial predisposition to neuropsychiatric disorders or a congenital origin for brain damage frequently has a lower mental status than one whose palsy is on a traumatic basis.[7, 8] Intellect is usually lower in those with left-sided paralysis than with right-sided disabilities, and diplegics are usually of lower intelligence.[9] The presence of stigma of mental deficiency such as microcephaly or an unusually shaped skull, ears, or digits may be helpful in evaluation.[10]

Formal psychological tests are often not particularly satisfactory in evaluating intelligence in cerebral palsy, even when done by a competent psychologist with special experience using a battery of tests. In this study, 55 per cent of the children were above the borderline range of normal ability. Frequently the pediatrician, using his instinct along with a few simple psychological tests, can fairly well estimate the child's intellectual level.

During early life, the Gesell developmental schedules, along with the Gesell drawing tests, can be utilized as indicators of maturation. In older children, the Goodenough "Draw a Man" test or the Bender-Gestalt test not only measure intelligence but also give some insight into personality.[11]

At the Meeting Street School, statistical evidence has been found to indicate that it may be possible to predict mental level in cerebral palsied children by correlating data obtained from psychological tests with the history of onset of speaking two- or three-word sentences. If two- or three-word sentences are delayed after 30 months, then intelligence will be below the borderline level. This observation is presented with full knowledge that our data are inconclusive.[12] It is hoped, however, that it will stimulate investigators along this line, since simple observations like this, if proved valid with a large series of cases, will prove helpful in psychological evaluation of the cerebral palsied.

It is frequently overlooked that a brain-damaged child may be functioning at an intellectual level lower than his capabilities as a result of specific disabilities in perception or behavior. The behavioral component previously discussed is outstanding. Both perceptual and emotional disturbances can apparently depress intellectual functioning enough so as to give low values in formal testing situations.[13]

There are other valuable means of appraisal which can be utilized. Good evidence of normal intelligence is acceptance of the patient into a group of children with normal intelligence. Willingness of the patient to participate in and keep up with this group is another good criterion. The reports of experienced teachers who observe progress on specific items from a week-

to-week or month-to-month basis, and reports by parents who are emotionally able to accept the child and his problem can be useful adjuncts in evaluation.

TREATMENT

The major responsibility of the pediatrician who is treating a child with cerebral palsy is the preparation of both parents and child for the long and vigorous treatment and training course which lies ahead. Since the primary consideration is the habilitation of the child and family for some measure of normal living, it is important to consider the problem as a whole rather than as purely a medical one. Since the success of any treatment plan involving children depends upon the establishment of a proper parents-physician relationship, a necessary axiom should be "parents come first." Since this philosophy is frequently difficult for the physician to accept, it seems wise to discuss some basic concepts concerning the mother-child relationship which clarify the basis for such an approach.

During the early years especially, a mother unconsciously regards her child as an image or extension of herself. Naturally, at first she strongly resents any inference that her child is imperfect since it infers that she too is imperfect. This in turn results in hostility toward the child, both because he is a problem and also because having such a malformed child diminishes her self-regard. Since it is not acceptable to the mother to feel this way about her offspring, the resentment is ofter transmuted into its apparent opposite. The mother goes to great extremes "to do everything" for the child, as if to deny her animosity and prove that she really loves him.[14]

This urge to do things for the child is reinforced by the deep need all mothers have, for their children to be dependent upon them. With children crippled such as these, the period of dependency is real and prolonged. While this may gratify some of the mother's needs, it may also have adverse effects upon the child and the mother as well.

For the palsied child, as well as for all other children, the period up to 7 years is exceedingly important in that basic and lasting psychological patterns are being made. If the mother can be helped to solve her emotional difficulties and requirements with and from the child before the conclusion of this period, then the child will be given an infinitely better opportunity to develop a normal working relationship with parents and society at large.[15]

Observations in office practice show that parents often go through three stages before they accept fully the help of the doctor. The first stage is hostility toward the physician on the part of the parents. They resent his confirmation of their deep fears concerning the child. Despite his knowledge of the frequency of this reaction, the physician must present the reality of the situation to the parents as soon as a diagnosis is made but in a way which is not cruel.

This can best be done by first giving the parents an opportunity to give their evaluation and estimate of the situation while sympathetically listening and helping to reinforce their basic understanding that something is wrong. This technique is much kinder than abruptly and authoritatively stating a diagnosis and giving pessimistic prognosis. Although it is not proper to offer false hope, one can with some

warrant afford to be tentative in the prognosis on the basis that there are some thing "we just don't know," and that medical advances are quite unpredictable.

The second stage consists of shopping from doctor to doctor. This should not arouse hostility in the family physician, since these parents soon realize that their problem is beyond the scope of medical magic and that reality was presented from the first.

The third stage is acceptance. When this is achieved then parents accept any progress, however slight it may be, as a token that their child will grow and can bring to them some form of happiness.

With patience and understanding of some of the psychological factors involved in every case of a crippled child, the pediatrician can win the parents' confidence and fulfill with credit the position of an advisor.

Preparation of the Child.—Just as parents must be prepared to accept a total training program, there are many major problems to be solved before many children can take part in the group program. Many youngsters with the intellectual capacity to profit from the training experience are unable to do so because of speech, vision, or hearing disabilities, convulsions, aberrant behavior. Remedial measures in these fields help the child make tremendous strides in over-all therapy. The specific concentrating or quieting effect of the amphetamine group, particularly in the child whose brain damage is the result of anoxia, is worthy of mention.[16] In some hyperactive retarded children, Tolserol may also have a beneficial quieting effect. This finding is based on preliminary studies.

During the first three years of life, parents are not so much concerned with the ultimate future of their crippled child as they are worried about progress with the immediate mechanical phases as standing, walking, or talking. During this period, the pediatrician may be overwhelmed by what he considers minor complaints regarding difficulties in eating or sleeping, temper tantrums, or uncontrollable crying. Actually, these complaints may be a reflection of the parents' deep emotional turmoil over the child, only focused and projected upon these apparently more acceptable physical details.

Convulsions of various types are not infrequent, but may go unrecognized in these infants. Proper anticonvulsive therapy may have a beneficial symptomatic effect which permits an early initiation of formal treatment.

Treatment.—There is no need in this paper to discuss actual treatment techniques in cerebral palsy since this has been outlined in recent texts.[17, 18] In the total training-treatment approach, the pediatrician by virtue of his special training and interest must act as a nucleus around which orthopedic, neurological and psychiatric guidance is woven into the skillful patterns achieved by the many therapists involved in the program. The pediatrician who can maintain a warm relationship with the parents, coordinate the requirements of the specialists, and not lose sight of the ultimate needs of the child has worthily fulfilled the role he holds in the cerebral palsy team.

SUMMARY

1. Criteria for evaluating the physical, mental, and emotional aspects of cerebral palsy in early life have been presented in a manner which the pedi-

atrician can utilize in office practice.

2. The pediatrician's most important role in cerebral palsy is to gain and maintain the confidence of the parents since the ultimate success of any treatment-training program depends upon their cooperation and understanding.

REFERENCES

1. Langdon, M.: Meeting Street School, Crippled Child 27: 9, 1949.
2. Gesell, A., and Amatruda, C. S.: Developmental Diagnosis, ed. 2, New York, 1947, Paul B. Hoeber, chaps. 3, 11.
3. Glass, B.: The Relation of Rh Incompatibility to Abortion, Am. J. Obst. & Gynec. 57: 323, 1949.
4. Knap, C.: The Dynamics of Newly Born Babies, J. PEDIAT. 29: 721, 1946.
5. Strauss, A. A., and Lehtinen, L. E.: Psychopathology and Education of the Brain-Injured Child, New York, 1947, Grune and Stratton, chap. 7.
6. Rosenfeld, G., and Bradley, C.: Childhood Behavior Sequellae of Asphyxia in Infancy, Pediatrics 2: 74, 1948.
7. Yannet, H., and McGovern, J.: Asymmetric Spastic Infantile Cerebral Palsy, Am. J. Dis. Child. 74: 121, 1947.
8. Yannet, H.: Infantile Cerebral Palsy With Severe Mental Deficiency, Pediatrics 3: 820, 1949.
9. McIntire, J. T.: A Study of the Distribution of Physical Handicaps and Mental Diagnosis in Cerebral Palsied Children, Am. J. Ment. Deficiency 51: 624, 1947.
10. Tredgold, A. F.: A Textbook of Mental Deficiency, ed. 7, London, 1949, Baillière, Tindall & Cox, chap. I.
11. Silver, A. A.: Psychologic Aspects of Pediatrics, Diagnostic Value of Three Drawing Tests for Children, J. PEDIAT. 37: 129, 1950.
12. Denhoff, E.: Needs in the Field of Psychological Appraisal of Children With Cerebral Palsy, New England M. J. 243: 524, 1950.
13. Bakwin, H.: Psychologic Aspects of Pediatrics, Feeble-Mindedness and Pseudofeeble-mindedness, J. PEDIAT. 37: 271, 1950.
14. Wright, D.: Personal communication.
15. Laufer, M.: Personal communication.
16. Bradley, C.: Benzedrine and Dexedrine in the Treatment of Children's Behavior Disorders, Pediatrics 5: 38, 1950.
17. Pohl, John F.: Cerebral Palsy, ed. 1, St. Paul, Minn., 1950, Bruce Publishing Co.
18. Egel, Paula F.: Technique of Treatment for the Cerebral Palsy Child, ed. 1, St. Louis, 1948, The C. V. Mosby Co.

Clinical Conference

CONFERENCE AT THE UNIVERSITY OF ARKANSAS HOSPITAL*

WILLIAM A. REILLY, PROFESSOR AND HEAD OF PEDIATRICS

Case 1. Massive Hematemesis—Possible Telangiectasis

DR. WILBUR G. LAWSON (Resident in Pediatrics).—(D. S. A-14980) This patient, a 12-year-old white female, was admitted Jan. 5, 1951, with a history of recurrent massive hematemeses during the previous ten days. Twelve days before admission the patient jumped from a horse, landing heavily on her feet, but without evident trauma. During the following day she was lethargic and complained of mild upper abdominal discomfort. Soon after supper on the third day, she suddenly vomited a small amount of fresh blood. This recurred the following morning and she was hospitalized at a hospital near her home. She was afebrile, hemoglobin was down to 56 per cent, and the white blood count was 15,950, with a normal differential. Chest x-ray, bleeding, clotting, prothrombin times and platelet counts were normal. There was no external evidence of hemorrhagic phenomenon. Intravenous feedings, sedation, and 1,500 c.c. blood transfusion was begun immediately after admission as she had vomited 1,800 c.c. of grossly bloody vomitus soon after admission. Three days later she lost 2,500 c.c. of bloody vomitus and received an equivalent amount of blood intravenously. Penicillin was given during the remainder of the stay there because of one febrile spike to 104° F. Another 1,000 c.c. of blood were lost on Jan. 2. The red blood count was brought from 2.9 to 4 million with transfusions the day before transfer to this hospital. A post-transfusion urticaria was controlled with 50 mg. of Benadryl. One tarry bowel movement was noted while in the hospital.

The patient's past history revealed she had had diphtheria, measles, whooping cough, and mumps in her early childhood. She had several immunizations at school, type unknown to the mother, and tonsillectomy in 1946, without untoward bleeding. However, the parents had noticed small bits of blood on her mouth, after arising, on several occasions in the two months before onset of the present illness.

Initial examination was not contributory. She was afebrile, blood pressure was 114/70, and she had a pale, sallow complexion. There were a few nodes in the right axilla. The abdomen was soft, nontender, and without palpable masses. The liver was down 1.5 cm. below the costal margin and the spleen was not palpable.

Laboratory results showed hemoglobin 9.5 Gm., red blood count 4.3 million, white blood count 9,000, with a normal differential and platelets 372,000. Bleeding time was one minute and clotting time two minutes, prothrombin time was 100 per cent of normal. Gastric analysis later showed normal free and combined

*Journal Series No. 924, University of Arkansas.

acidity. A bone marrow examination revealed only normoblastic hyperplasia, i.e., a reactive marrow.

Transfusions, morphine sedation, and vitamin K were begun after admission and no further hematemesis was observed for four days. During this time the hemoglobin was raised to 14 Gm. A Sippy diet was then started and tolerated well. However, tarry stools began to appear. A barium swallow and gastrointestinal series were done on the fourth day with significant findings. Large mobile masses were seen and thought to be blood clots. Four hours after this procedure massive hematemesis recurred, and after transfusion an exploratory laparotomy was done by Dr. James H. Growdon.

In the stomach there were innumerable 1 to 2 mm. areas of submucosal extravasated blood which oozed constantly. These were found to be most numerous in the region of the lower antrum. A few enlarged mesenteric nodes were found and pathological section revealed "reticuloendothelial hyperplasia." The hemorrhagic areas in the stomach were not biopsied.

No feedings were attempted until the third postoperative day, and during this time alternate aspiration and instillation of topical thrombin solution was done through a Levine tube. Transfusions were continued and a Sippy diet again started on the third postoperative day and tolerated well. She was able to take a soft diet on the seventh day. The stools were tarry for twelve days and gradually cleared. No further hematemesis occurred. Proctoscopic examination showed a normal mucosa. She was discharged twenty-six days after operation on a soft diet with supplementary strained meat and vitamins. At the time of check-up, five weeks after discharge, she was taking the diet well and was asymptomatic. The hemoglobin was 11.5 Gm.

DR. REILLY.—Acute massive hematemesis such as exhibited by this patient is an uncommon emergency in pediatric practice. One must deal quickly with the ensuing shock state and delay definitive diagnostic procedures unless an obvious etiology presents itself. This case was of such obscure nature that specific diagnosis is still lacking.

DR. GROWDON (Associate Professor of Surgery).—While massive upper gastrointestinal hemorrhage is relatively uncommon in this age group, the problems of management are much the same as in adults. With the exception of certain malignant tumors, the etiological factors are quite similar. Most patients will respond satisfactorily to nonsurgical care but blood volume should be replaced promptly by whole blood transfusions to prevent the complications of prolonged shock and to have the patient ready for surgical intervention should bleeding continue. Roentgenological examination of the upper gastrointestinal tract using contrast media should be performed as soon as the patient's condition permits so that an accurate diagnosis can be made, if possible. In this instance we could find no abnormalities following this procedure. We felt compelled to subject this patient to exploratory laparotomy because of repeated exsanguinating hemorrhages. Operation accomplished nothing beyond establishing a possible diagnosis.

We are extremely reluctant to perform an operation for acute upper gastrointestinal bleeding unless an accurate diagnosis can be made preoperatively and esophageal varices, in particular, can be excluded.

DR. LAWSON.—Immediate considerations included acute gastric ulcer, trauma inflicted by the fall, blood dyscrasias, Banti's syndrome with ruptured esophageal varices. The history was of value primarily in exclusion, as the patient had enjoyed excellent health. There was no evidence of digestive disturbance, epigastric pain, or vomiting in the past. The "fall" was reliably described by the parents as being of little consequence and certainly not severe enough to have produced the extreme state of the child. There had been no preceding weakness, pallor, pain, fever, anorexia, or bleeding to suggest a blood dyscrasia. The liver and spleen were not enlarged, and abdominal prominence was lacking; there was no purpura or bruising to implicate either blood dyscrasia or Banti's syndrome. The platelet count, bleeding time, and clot retraction were normal, and the differential white count also was against blood dyscrasia. There was no indication to consider poison ingestion, and the nutritional status was such that contributory nutritional deficiencies were not considered. We are now concerned about the more obscure syndrome clarified by Osler in 1901, of hereditary telangiectasia.

DR. REILLY.—Osler-Weber-Rendu[1, 2] disease does have a very strong hereditary trait but may disappear in several generations of a family and then may reappear suddenly. The tiny groups of dilated capillaries may be distributed in most any organ system solely or in association with lesions in other systems. They more commonly affect the skin of the face, chest, abdomen, and mucous membranes of the nose and mouth. They are easily traumatized and bleed freely. Occurrence in the gastric mucosa without other lesions has been described a number of times and always as a finding in a case of obscure hematemesis. It is not always possible to trace a hereditary link. The family history and their superficial examinations were negative. Cases previously described had millet-sized areas of ulceration with small bits of blood oozing freely. No absolute treatment other than cauterization of the individual lesion has been evolved. The use of rutin was encouraging to some clinicians in recent years but has not obtained general acceptance. However, it would be well to try this drug if this patient develops recurrences in the future. I believe this is one of the youngest patients with massive gastric hemorrhage if it be telangiectasia.

Case 2. The Use of ACTH in Hemolytic Disease of the Newborn (Erythroblastosis Fetalis)

DR. LAWSON.—(P. D. A-14128) This patient is a white female infant, now 3 months of age, who was the product of the sixth pregnancy of an Rh-negative mother, Rh-positive father. Previous pregnancies had resulted in a normal Rh-negative sibling, two Rh-positive infants, and the fourth pregnancy was interrupted by spontaneous abortion. A transfusion, given to the mother because of excessive blood loss, was followed by a reaction. The

next child, now 18 months of age, was normal and is Rh negative.

During the last trimester of the present patient's gestational period, the mother's quantitative Coombs titer rose rapidly and reached 1020 units one week prior to delivery. Labor was induced two days before the expected date of confinement and uneventful spontaneous delivery occurred under saddle block anesthesia. The birth weight was 7 pounds; she was normally active but moderately icteric at birth and showed yellow staining of the cord structures and vernix. The liver extended 4.5 cm. and the spleen 3 cm. below the costal margin. The placenta weighed 2,250 grams. Laboratory findings from cord blood were hemoglobin 8 Gm., red blood count 2.10 million, white blood count 69,000, with 267 nucleated red blood cells per cubic millimeter. The Coombs test was strongly positive and a capillary hemoglobin again one hour later was 9.5 Gm.

Immediately after the latter determination 5 mg. of ACTH was given subcutaneously and repeated every six hours for the first five days (20 mg. per day). Preparations for exchange transfusion were completed for precautionary reasons, but no blood was administered until after seventy-two hours. Vitamins C and K and penicillin were given in usual doses.

During the five-day test period twenty blood counts were done, initially at two-hour intervals and later at eight-hour intervals. Findings may be summarized by saying that the hemoglobin remained at 9 Gm. (±0.5 Gm.) for seventy-two hours, at which time the observations were interrupted by starting blood transfusions. Nucleated red blood cell counts rose from the initial 43,840 to a maximum of 86,595 at twenty-four hours, at which time the total white blood cell count was 131,000 per cubic millimeter. The nucleated red cells fell rapidly after forty-eight hours and were gone by the fifth day of life (white blood count 8,800). The hemoglobin was raised gradually by small daily transfusions to 12 Gm. before discharge.

Jaundice was rather marked by the second day but the patient never exhibited depression, spasticity, or cerebral cry, and the appetite was good. There was a normal Moro. A weight loss of 15 ounces occurred. The patient was afebrile. By the fifth day the liver was only 3 cm. down and the spleen was just palpable.

ACTH treatment was discontinued on the fifth day and transfusions continued, only 105 c.c. of type O, Rh-negative blood being used for the five transfusions.

Three days after stopping ACTH the jaundice was obviously recurring and the liver was enlarged to 4.5 cm. The spleen was only slightly enlarged. This mild exacerbation improved during the following five days without sequelae.

Follow-up examination at one and two months showed weight gains to 7 pounds, 14 ounces and 9 pounds, 1 ounce, respectively. The hemoglobin was 9.5 Gm. on each occasion. Developmental progress is normal and the liver and spleen are of normal size.

DR. BARNETT P. BRIGGS (Associate Professor of Pediatrics).—What are the reasons for giving ACTH?

DR. LAWSON.—The pathology of erythroblastosis fetalis is recognized as resulting from the destruction of fetal erythrocytes by the action of anti-Rh agglutinin. This reaction is heightened by each succeeding pregnancy productive of an Rh-positive fetus, regardless whether it is carried to term or not; this was the sixth pregnancy. ACTH has been thought to block other antigen-antibody reactions and it was with that property that we were concerned. By blocking further reaction between anti-Rh agglutinin and the fetal erythrocytes, it was hoped that further hemolysis might be avoided until the agglutinins were excreted by the usual route.

Complications of the icterus gravis group, such as kernicterus, hemorrhage, and liver damage, occur within the first five days of life and thus bring the early care of the erythroblastotic infant into greatest importance. An infant surviving the initial danger period without complications may be expected to recover with multiple transfusions.

DR. ALICE G. BEARD (Assistant Professor of Pediatrics).—Exchange transfusion has become accepted treatment with this condition, with very good results. Why would this not have been as good?

DR. REILLY.—We were prepared to perform replacement transfusion as soon as it might become necessary. However, if an agent, such as ACTH, might allow maintenance of a stable blood count and prevent the accompanying sequelae, one might then use multiple single transfusions to restore blood deficit without the attendant dangers and added difficulties of exchange. This would be of great value to doctors in remote communities unable to carry out technically the more involved replacement transfusion.

DR. SAM PHILLIPS (Associate Professor of Pediatrics).—How would you evaluate the results of this case?

DR. REILLY.—One case does not permit evaluation. We can only state that a patient, fulfilling the criteria for a severe erythroblastosis of a combined icterus gravis-anemia type, was able to maintain a stable hemoglobin, lose the jaundice, and avoid all complications while receiving ACTH alone. This in no way replaces eventual transfusion, but only offers a hope for simplification of treatment and possibly an improved prognosis. Further trial is necessary. Correspondence with other medical centers using larger dosages of ACTH, however, does not confirm this hope.

Case 3. Results of Streptomycin Therapy in Twenty-Nine Patients With Tuberculous Meningitis

DR. LUTHER R. WHITE (Resident in Pediatrics).—(T. MacF. 94709) This patient is a 4-year-old white male, admitted Dec. 25, 1948, who developed fever and lethargy three weeks previously. Projectile vomiting and nonproductive cough occurred during the week prior to admission. The mother had tuberculous adenitis eleven years before, at which time her father died of pulmonary tuberculosis. Repeated chest films on the mother over a ten-year period, the last one a year before the patient's illness, were negative. She has had normal health.

On examination the patient was quite thin and had nuchal rigidity without other significant physical findings. The diagnosis of tubercu-

lous meningitis was confirmed by a strongly positive tuberculin skin test and positive smears and cultures of the spinal fluid on two occasions. Chest x-rays revealed bilateral hilar lymphadenopathy, which was noted to regress during the course of treatment.

Streptomycin, 250 mg. intramuscularly every six hours, without Promizole was given for twenty-four weeks; intrathecal streptomycin, 25 mg., every other day for five doses, was given.

Low-grade fever, never over 100.4° rectally, and lethargy continued for three weeks after treatment was started. After this time he became more alert and appetite improved. The right arm and leg were then noticeably spastic. Pleocytosis, up to 200 cells, continued for three months.

At discharge he was unable to walk or talk, and the spasticity was quite marked. He was overactive, temperamental, and retarded. An electroencephalogram done nine months after treatment showed abnormally slow activity with negative spikes in the left antero-tempero-parietal area, interpreted as residual encephalitis. There was some residual hilar lymphadenopathy in the chest. By this time he was ambulatory and a severe behavior problem.

One year after treatment was stopped his spinal fluid was entirely normal. His IQ was 53. Then petit mal seizures, two to eight daily, developed. A pneumoencephalogram done one month later showed a grossly dilated left ventricle with cortical atrophy.

At present, 18 months after finishing therapy, his conditions is as follows: general nutrition continues to be excellent but he is constantly restless, inattentive, and retarded; moderate residual spasticity is present in the right arm and leg with slight muscle atrophy; the petit mal seizures have diminished in frequency after the pneumoencephalogram, but he frequently has severe falls due to difficulty in running. For some months now he does not have seizures and has not used a sedative.

Dr. Alexander M. Earle (Assistant Professor of Pediatrics).—In general, our therapy was as follows: streptomycin or dihydrostreptomycin was given intramuscularly in doses of 50 to 80 mg. per kilogram, divided into four doses daily. This was to be continued for 180 days between March, 1948, and July, 1949. Thereafter only dihydrostreptomycin was given and that in the muscles. Streptomycin was given intrathecally in doses of 25 to 50 mg., daily at first, then every other day for twenty-five to forty injections. Promizole, in 1 to 2 Gm. daily doses, orally at six-hour intervals, was given for six months, when purchasable. (Ten patients received Promizole, two of the living patients received it and two did not.)

The patient presented (T. MacF.) is an example of the sequelae in one of the children treated supposedly enough to arrest tuberculous meningitis between March, 1948, and August, 1950. Thirty-five patients were positively diagnosed. Only twenty-nine could be started on therapy. Of these treated ten died during the first month, five during the second month, two during the third month, and three before the sixth month of therapy. Five died after discharge and

TABLE I. TUBERCULOUS MENINGITIS—PATIENTS TREATED 3+ MONTHS*

NAME NO.	AGE	SEX COLOR	DURATION OF DISEASE BEFORE THERAPY (DAYS)	THERAPY D.	THERAPY ST.	THERAPY PRO.	DURATION (DAYS)	SPINAL FLUID END OF THERAPY	PHYSICAL AND MENTAL STATUS END OF THERAPY	TUBERCULOSIS ARRESTED	DAYS DIED AFTER BEGINNING THERAPY	COMMENTS
B. S. 108286	16 mo.	F W	8	IM.	IT.	Yes	93	253 cells 91 P. 110 L. 160 mg. Pr.	Spastic	No	0	Died while on therapy.
J. S. 83589	13 mo.	M N	5		IM.	0	118	615 cells 418 P. 197 L. 162 mg. Pr.	Spastic	Temporary	81	Died at home.
J. W. 87185	23 yr.	F W	7		IT. IM.	0	122	190 cells 75 P. 115 L. 97 mg. Pr.	Spastic legs	No	0	Died while on therapy. Active tuberculous (pulmonary, renal, and meningeal).
I. B. 93512	21 mo.	F W	7		IM. IT.	Yes	135	346 cells 80 P. 266 L. 920 mg. Pr.	Spastic	Temporary	18	Died at home.
B. G. 99147	3 yr.	M W	14		IM.	0	150	132 cells 36 P. 96 L. 96 L.	Spastic	Temporary	33	Died at home.
A. H. 103606	2 yr.	M N	9		IM. IT.	Yes	180	28 cells 14 P. 14 L. 49 mg. Pr.	Left hemiplegia; mentally alert	Temporary	18	Died at home.

B. W. A-2973	10 yr.	M W	21		IM. IT.	Yes	180	175 cells 20 P. 80 L.	Comatose Spastic	No	0	Died while on therapy. Healing tuberculous meningitis, healed pulmonary tuberculous—autopsy.
M. U. A-10267	6 mo.	F W	12		IM. IT.	0	240	392 cells 178 P. 214 L. 1200 mg. Pr.	Treated in California 8 months	Temporary	135	Relapsed acute meningitis hydrocephalus—autopsy.
J. G. A-5981	6 mo.	M W	10	IM.	IT.	Yes	150	30 cells 4 P. 26 L. 52 mg. Pr.	Hydrocephalus Spastic and mental retard.	Yes		Therapy discontinued. Alive since 11/10/50.
P. A. 90247	1 yr.	F W	12		IM. IT.	0	165	2 cells 70 mg. Pr. 75 mg. S.	Hydrocephalus Spastic mental retard.	Yes		Alive since 1/21/50.
W. E. A-2711	2 yr.	M N	14		IM. IT.	Yes	182	2 cells 88 mg. Pr. 49 mg. S.	Hydrocephalus Spastic mental retard.	Yes		Alive since 11/14/50.
T. MacF. 94709	4 yr.	M W	21		IM. IT.	0	180	0 cells	Hydrocephalus Spastic—right mental retard.	Yes		Alive since 6/16/49.

*Abbreviations

D.—Dihydrostreptomycin.
IM.—Intramuscularly.
IT.—Intrathecally.
L.—Lymphocytes.
N.—Negro.
P.—Polymorphonuclear.
Pr.—Protein.
Pro.—Promizole.
retard.—Retardation
S.—Sugar
St.—Streptomycin.

four are now alive. The mortality was 86 per cent in all treated patients; disregarding those treated for less than one month, it was 78 per cent; for those treated over five months, it was 50 per cent.

The patient just presented has attained one of our best results of the four patients now alive (Table I) but he is mentally retarded, has spasticity, and had petit mal attacks. The other three patients also have mental retardation, spasticity, and hydrocephalus; the electroencephalograms show abnormal tracings. Their psychological examinations show severe retardation affecting motor and language development. The associated pulmonary findings in these four have changed as follows: T. MacF., nodulation, which disappeared after treatment; W. E., miliary lesions which showed some clearing; P. A., a confluent density in one lobe shows great clearing; J. G., a confluent density in one lobe before has almost entirely disappeared.

Ten of the twenty-nine treated patients had an associated pulmonary miliary tuberculosis; nine of these have died and one case, W. E., who is still alive, has shown clearing of the nodular densities but there is still evidence of increased pulmonary markings.

Twenty of the twenty-nine patients had positive spinal fluid cultures for *Mycobacterium tuberculosis*. Nineteen had positive tuberculin reactions and three had negative reactions. In seven the tuberculin test could not be completed.

Toxicity from drugs was of minor degree.

DR. REILLY.—We are not satisfied with these results, particularly the mental retardation. We wonder if such therapy is justified, or what type of therapy is best for a given case, starting any type of case on treatment as we often had to do. Of others previously using the same type of therapy as we use here, none has reported[3] better results, particularly in regard to the mental status.

REFERENCES

1. Osler, W.: On a Family Form of Recurring Epistaxis, Associated With Multiple Telangiectases of the Skin and Mucous Membranes, Bull. Johns Hopkins Hosp. 12: 333, 1901.
2. Kushlan, S. D.: Gastrointestinal Bleeding in Hereditary Hemorrhagic Telangiectasis, Gastroenterology 7: 199, 1946.
3. Lincoln, E. M., and Kirmse, T. W.: Chemotherapy of Tuberculosis in Children, Pediatrics 5: 280, 1950.

Psychologic Aspects of Pediatrics

THE HOSPITAL CARE OF INFANTS AND CHILDREN

HARRY BAKWIN, M.D.
NEW YORK, N. Y.

THE disadvantages of hospitals for the care of children are numerous. The hazards of cross-infection are well known and by no means all hospital infections respond readily to the antimicrobic agents. The child is often terrified by the prospect of leaving his home and being turned over to strangers. Parental anxiety is increased when a sick child is out of the sight of his parents. Hospitals subordinate the responsibility of parents and diminish maternal skills and confidence. In addition they interfere with the sense of satisfaction which a mother gets from having successfully nursed her child through a serious illness. Hospital care is expensive.

INFANTS[1, 2]

Infants are necessarily difficult to care for in hospitals. During the early months of life babies are entirely dependent on their environment for the gratification of their needs, physical, emotional, and, to a large extent, motor. They are unable to indicate satisfactorily when they are hungry and when they have had too much and it is hardly possible for the nurses to understand the idiosyncracies of the individual infant on short acquaintance. Moreover the method of prescribing food lacks the flexibility which is possible in the home. Precise orders for feeding are given and there is no mechanism by which the infant can have more of his formula at one feeding when he is hungry and less at another when he is satisfied. Food refused at one feeding cannot be made up at another.

Of major significance for the infant is the isolation to which he is subjected in the hospital.[3] Unlike the older child or the adult who can fill his lonely hours with memories of the past and plans for the future, the infant has no mental or emotional resources within himself on which he can draw. All stimulation must come from without; yet there is little or none forthcoming in most hospitals. Indeed, it is generally considered that proper isolation against infection requires that manipulations be limited to those necessary for physical care.

Infections, mainly of the nose, throat, and ears, are certainly frequent in infant wards and, though mild in themselves, they often have disastrous consequences in that the infants may stop eating, vomit and develop diarrhea, lose weight, and eventually die. For the prevention of cross-infections, isolation has been regarded as the principal effective measure. Consequently, infants in hospitals are as a rule handled only when necessary and visiting by parents is kept at a minimum.

The importance of cross-infections, though unquestionably considerable, has been exaggerated. For over twenty years the sick babies at Bellevue Hospital have been handled freely by nurses, physicians, and students, and visiting hours for parents have

From the Department of Pediatrics, College of Medicine, New York University-Bellevue Medical Center.

been increased. Despite this greater freedom the cross-infection rate has decreased rather than increased and the case fatality rate for infants under one year of age has fallen during this period to about one-fourth its previous level. More than half of the drop took place before antimicrobic therapy was introduced in the late thirties. The principal lethal factor previously was psychologic neglect, not infection; and efforts to protect babies against infection by isolating them intensified the emotional deprivation.

Babies, and children as well, should be admitted to hospitals only after careful consideration of the nature of the illness and the type of home. Even a very humble home is often better suited to the care of the child and less upsetting to the parents than the hospital with all its elaborate equipment. Spence remarks that, "As a doctor's experience increases the fewer are the children he confines to hospitals." Children should be returned to the home as soon as possible. It is unwise to keep a baby in the hospital, after he has recovered from his original ailment, until he starts to gain weight. In the large majority of instances he will thrive much better in the home.

Efforts should be made to humanize the care of infants in hospitals. Nurses should regard themselves as substitute mothers, and mothering and cuddling should be as much a part of nursing care as bathing, dressing, giving treatments, and so on. Nurses and interns should be encouraged to pick up and play with the babies during their free moments. Infants who must remain in the hospital for prolonged periods may be assigned to particular nurses or interns for their special care. Parents should be permitted to visit their infants as often as is compatible with ward routine and should be encouraged to hold and fondle them. When some painful procedure is carried out, such as a venipuncture, the infant should be held in the nurse's arms for a few moments afterward, to be comforted and reassured. Infants, before they were able to eat by themselves, should be held in the nurse's arms while feeding, duplicating the position used during breast feeding. Crying infants need the same sort of attention as in the home. An effort should be made to discover the reason for the crying and to correct it.

In selected cases it is wise to invite the mother to come and spend the day with her baby and take over his care. Most mothers quickly adjust to ward routine and become helpful. Often they not only relieve the nurses of the care of their own child but they help with a little neighbor as well.

Spence[4] recommends that mothers be admitted to the hospital with their babies. He says, "The most difficult and time-absorbing task in nursing is the care of the youngest children, who must be nursed, fed, and changed at frequent intervals of the night and day. If in addition there is much technical treatment the care of one seriously ill infant becomes one woman's work. If there must be off-duty periods, it will be two women's work. If we introduce the three-shift system, it will be three women's work. While these infants are in hospital their mothers are at home suspended in anxiety. It would seem logical, therefore, that a solution of the problem should be found in admitting the mothers to the hospital to nurse their

own children. This is no theoretical proposal. I have worked under this arrangement in my hospitals for many years, and I count it an indispensable part of nursing in a children's unit. Nor is it a revolutionary idea. By far the greater part of sick children's nursing is already done by mothers in their homes, and the mother's nursing unit is merely an extension of this responsibility. Not all illnesses will be suited to this nursing, but the majority of all children under the age of 3 derive benefit from it. The mother lives in the same room with her child. She needs little or no off-duty time, because the sleep requirements of a mother fall near to zero when her own child is acutely ill. She feeds the child; she tends the child; she keeps it in its most comfortable posture, whether on its pillow or on her knee. The sister and nurse are at hand to help and to administer technical treatment to the child.

"The advantages of the system are fourfold. It is an advantage to the child. It is an advantage to the mother, for to have undergone this experience and to have felt that she has been responsible for her own child's recovery establishes a relationship with her child and confidence in herself which bodes well for the future. It is an advantage to the nurses, who learn by contact with the best of these women, not only about the handling of a child but about life itself. It is an advantage to the other children in the ward, for whose care more nursing time is liberated. In teaching hospitals it is of further advantage to the students, who gain a practical experience of the form of nursing they will depend on in their practices and learn to recognize the anxieties and courage which bind the mothers to their children during illness: a lesson which fosters the courtesy on which the practice of medicine depends. I advocate this method of nursing, not on sentimental grounds but on the practical grounds of efficiency and necessity. Apart from all other reasons the shortage of nurses will impose this method on us in the future."

The practice of housing the mother in the hospital with her sick child has been carried out by Spence for many years in the large university hospital in Newcastle-on-Tyne. This is also the custom in some university hospitals on the Continent. Spence finds it particularly well suited for surgical patients who must be in the hospital for about a week. It is a humane, happy, and satisfactory method of nursing sick children.

It has been the custom at the Bassam Clinic,[5] a surgical hospital in New Zealand, to admit each mother with her baby to a small bed-sitting room of her own. Here the mother can look after her baby exactly as though she were at home. She has the companionship of other mothers in neighboring rooms and she can enjoy the garden where the babies take the air in their baby carriages. Surgical dressings are done aseptically, generally under light anesthesia to reduce emotional shock. The mother does all the routine work for the baby such as feeding, dressing, changing diapers, thereby saving much time for the nurses. A survey after the clinic had been running for five years showed that there had not been a single case of cross-infection, local or general, and not a single slough or case of dehiscence.

Infants should be kept outdoors as much as possible. They have better color, they eat and sleep better, and they seem more contented. The mechanisms which make outdoor treatment beneficial are intricate and are probably dependent on psychologic as well as physical factors.

Whiny, unhappy infants need special attention. Their demanding attitude often antagonizes the ward personnel and they are consequently ignored while the happy, pleasant child, who needs no extra affection gets a great deal of it. It is, therefore, advisable to assign them to particular nurses or interns for special attention.

Often the unhappy child at first resents the advances of friendly adults and pushes away all who try to approach him. This negativistic phase is short-lived. If the baby is allowed a two- or three-day period during which he is treated pleasantly but rather casually, a personal approach can be begun. The results obtained by giving these children affection and attention are excellent and within the short space of a week or two, often sooner, a definite and striking improvement in behavior can be expected.

The elimination of useless procedures such as the daily administration of vitamins (which may be given at weekly or longer intervals), the frequent temperature takings and weighings, the needless use of nose drops, the elaborate record keeping and the, in the main, meaningless nurses' notes will give the nurses free time which can be better spent attending to the psychologic needs of their charges. In many institutions, "play ladies" do an excellent job entertaining the infants and children.

Infants with eczema require more attention and manipulation that others since, when left by themselves, they scratch more.

History taking in the age group 1 to 3 or 4 years should include information about training procedures and their success or failure. It is customary in most hospitals to bathe, dress, and feed the young child (instead of letting him learn to do these things for himself) and then to disregard him. If the infants are to remain in the hospital for a long time and are not too sick, training for self-feeding, toilet, and so on is necessary just as in the home. If a child has been trained to the toilet it is wise to ask whether he has been taught to use substitute words to indicate when he has to go. Such words may be confusing, as in the case of a little girl who wet and soiled for three days because no one understood what she meant when she said she had to "make bubbles."

The history should also contain information about habits such as finger-sucking and these should be discussed with the parents.

THE SCHOOL-AGE CHILD[6]

The school-age child in the hospital is beset by many worries. He is concerned about the nature and outcome of his particular illness and often feels that he is in some way at fault for having it. If he is to stay in the hospital for any length of time loss of school work becomes a prominent source of concern. Other considerations are a feeling of being different from other children, the enforced physical inactivity, worry about what is going on at home, a feeling of being deserted or rejected.

The child who is confined to bed suffers a great disadvantage in that he is unable to release pent-up emotions by physical activity. The normally active child "blows off steam," when he is angry or otherwise agitated, by rushing about in play; just as the angry adult relieves himself by banging a table, stamping the foot, slamming a door, or going out and chopping wood. Obviously these outlets are not open to the child whose activity is restricted.

The special problems of the child with tuberculosis and the child with rheumatic fever have been discussed previously in the JOURNAL.[7, 8]

Older children are usually happier when they can see other children about them. They learn much through imitation and their behavior is likely to be patterned after that of the other children. They should be expected to take certain responsibilities commensurate with their age and health, to feed themselves, ask for the bedpan, not to jump about, to be quiet when being examined, and so on. They should understand that there is a routine in the hospital into which they must fit. Young children should be provided with entertainment in the form of picture books, crayons, beads for stringing. They should have the opportunity for conversation.

A cheerful atmosphere can be created by suitable frescoes, birds, fish bowls, turtles, snails.

School-age children do better when they understand what is going on about them. They should therefore receive some information about their illnesses and what treatment to expect. Their questions should be answered sympathetically.

Great care is necessary in discussing the child's illness in his presence. Children understand much more than is appreciated and they are easily made apprehensive. No matter how aware one may be of the reaction of the patient, it is well-nigh impossible to conduct bedside teaching without disturbing the child. What to the physician is a "good murmur" or an "interesting diastolic" is likely to be a source of great anxiety to an intelligent child who has heard murmurs discussed, not only at his own bedside, but at the bedsides of his neighbors. Many children acquire a surprising knowledge of the significance of the different physical signs and symptoms. Extreme caution is necessary. Interspersing encouraging comments to the interns and students, which are intended for the ears of the child, help to allay anxiety.

When the child first enters a ward, the nurse-in-charge should introduce herself: "I am Miss So-and-so. This is Mary (the maid). If you want anything, call her or me."

In presenting patients for discussion, students and interns should refer to the children by name, as: Johnny Jones is an alert, little boy, 3 years of age, instead of: This is a 3-year-old white male. The mother, if present, is addressed by name. If it is necessary to discuss the child's condition in his own presence or in the presence of the parents, due consideration should be given to their reactions.

In some hospitals mental tests and electroencephalography are done in the psychiatric division. A trip to "psycho" is upsetting to most intelligent children.

Hospital wards should be provided with a suitable room where the doctor

can talk to the parents without distractions. The intern must understand that this is an essential part of his training and not a chore to be avoided. The visiting staff should participate in this part of the training program. Before a child is discharged from the hospital the physician will do well to sit down with the parents and give them some explanation of the nature of the illness, the outlook for the future, and the need, if any, for future observation or treatment.

A telephone hour should be set aside each day when parents can speak to the house-officer about their children.

Not uncommonly children who are generally quite well behaved become greatly upset when the parents leave after a visit. Despite this most physicians feel that children should be visited by their parents regularly. Some parents make matters worse by slipping away while the child is otherwise engaged, or by saying they will be right back and then leaving, and so on. Such behavior is resented by the children and should be discouraged.

Children who react with anxiety when the parents leave should be comforted by a nurse or attendant whenever possible.

Painful or unsightly procedures should be carried out in a special room so as not to frighten the other children. The patients should not be permitted to see those sufferings of a very sick child or to witness death.

The training program for the house staff should be so organized that each house-officer spends at least one-half day a week in the out-patient department throughout his term of duty. In this way he has the opportunity of becoming acquainted with a certain number of families and he has the satisfaction of a personal relationship with his patients which is difficult to attain otherwise. Should it become necessary for a member of one of the families to enter the hospital, the parents and the child will feel much more comfortable, knowing that they have someone in the hospital who is interested in them. Knowing his families, the physician can better judge whether or not a sick child can be taken care of at the home or will need hospital care. Under proper guidance by the visiting staff, the intern comes to appreciate the meaning of illness not only for the patient but for the family as well.

With the convalescent or the chronically ill child time should be allotted for both work and play. Since the major concern of most school-age children is that they are falling behind in school work, it is wise to have them attend the hospital school or to have bedside teaching. If teachers are not available the mother or nurse may be able to follow the school assignment and see that the lessons are studied. Suitable books should be available for reading and various types of handiwork can be taught such as knitting, basket weaving, and bandage rolling for girls, and rug making, leather work, and simple carpentry for boys. Growing grass, carrots, yams, narcissus, hyacinth, and other plants in little paper cups is a source of delight to children. At the same time they have the responsibility for the care of the plants. At some institutions the children put out an illustrated newspaper. Celebrations or parties of a simple sort on special occasions or

holidays break the monotony and help greatly to brighten the hospital stay.

Smocks over the nurses' uniforms lends a schoolroom atmosphere to the hospital ward which is pleasing to most children.

PLAY LADIES

The "play ladies" or "toy ladies," as the children often call them, provide a most useful service in hospitals. They not only entertain the children, they are also helpful in the treatment of emotionally disturbed children. The house-officer in charge of the ward should meet with them regularly and discuss the patients with them. From time to time the visiting staff should attend these meetings.

The meetings serve a triple purpose: they provide an opportunity for the women to ask questions about the patients; the physician may point out the special play needs of individual patients; the women come to understand better the importance of their contribution and the fact that it is appreciated by the medical staff as well as the patients.

THE METABOLIC EFFECTS OF BED REST

The adverse metabolic effects of restricted activity should be duly weighed when a child is confined to bed. There takes place, within a few days, a loss of nitrogen, calcium, phosphorus and sulfur.[9] In addition restricted persons show a progressive failure of circulatory reflexes, which are necessary for the maintenance of an adequate circulation in the erect position, progressive generalized weakness, and easy fatigability.[10] Most of the studies have been made in adults. Johnston[11] has found similar losses of nitrogen and calcium in children confined to bed.

According to Harrison,[12] there is no proof that rest in bed, after the acute manifestations have subsided, is of any value to patients with congestive failure, myocardial infarction, or angina pectoris. He recommends, for all patients with severe forms of heart disease, activity below the threshold which produces symptoms like dyspnea, pain, fatigue. It has also been stated that there is no good evidence that recurrence of rheumatic fever results from activity.

In patients with active tuberculosis, improvement in the retention of nitrogen and calcium takes place during the early months of bed rest.[10] Continued too long, however, a decline in retention follows with improvement when moderate activity is introduced. Johnston explains these seemingly contradictory findings by the fact that patients, when first coming under treatment for active tuberculosis, have depleted stores which are replenished when bed rest is introduced. Later on, when replenishment has been accomplished, the decline incidental to inactivity asserts itself.

Dock[13] states that "The physician must always consider complete bed rest as a highly unphysiologic and definitely hazardous form of therapy, to be ordered only for specific indications and discontinued as early as possible."

REFERENCES

1. Brennemann, J.: The Infant Ward, Am. J. Dis. Child. 43: 577, 1932.
2. Grulee, C. C.: The Newborn, Am. J. Dis. Child. 58: 1, 1939.
3. Bakwin, H.: Loneliness in Infants, Am. J. Dis. Child. 63: 30, 1942.
4. Spence, J. C.: The Care of Children in Hospitals. The Charles West Lecture, delivered at the Royal College Physicians, Nov. 19, 1946.

5. Pickerill, C.: Nursing Mirror, Aug. 16, 1947, Supplement p. 11 quoted by Lancet 2: 588, 1947.
6. Powers, G. F.: Humanizing Hospital Experiences, Am. J. Dis. Child. 76: 365, 1948.
7. Bakwin, H.: The Child With Tuberculosis, J. PEDIAT. 37: 936, 1950.
8. Bakwin, H.: The Child With Rheumatic Fever, J. PEDIAT.
9. Cuthbertson, D. P.: The Influence of Prolonged Muscular Rest on Metabolism, Biochem. J. 23: 1328, 1929.
10. Deitrick, J. E., Whedon, G. D., and Shorr, E.: Effects of Immobilization Upon Various Metabolic and Physiologic Functions of Normal Men, Am. J. Med. 4: 3, 1948.
11. Johnston, J. A.: Factors Influencing Retention of Nitrogen and Calcium in Period of Growth, Am. J. Dis. Child. 80: 551, 1950.
12. Harrison, T. R.: Abuse of Rest as a Therapeutic Measure for Patients With Cardiovascular Disease, J. A. M. A. 125: 1075, 1944.
13. Dock, W.: The Evil Sequelae of Complete Bed Rest, J. A. M. A. 125: 1083, 1944.

Comments on Current Literature

KEROSENE POISONING

KEROSENE intoxication is an important clinical syndrome, particularly in young children, and usually follows attempts on the part of the small child to drink some of the liquid left within its reach inadvertently.

Chemically, kerosene is a hydrocarbon complex derived from crude oil or petroleum, and is composed of high boiling point fractions which are of relatively low volatility, varying according to the source.

The clinical manifestations of this intoxication syndrome are coughing and choking, often associated with rapid, grunting respiration, with subsequent fever, vomiting, lethargy, and, in some instances, convulsions. Physical examination reveals the presence of râles in the chest in approximately one-third of the cases, cyanosis in a tenth of the cases, and x-ray evidence of pneumonia in over three-fourths. The mortality is a significant one, ranging from 4 to 10 per cent in the reported cases.

The pathogenesis of kerosene intoxication has been the subject of a number of careful studies. There seems to be considerable difference of opinion as to whether the pulmonary damage, which constitutes the major feature of the poisoning, is the result of injury to the lung tissues via the hematogenous route, or whether aspiration of the kerosene is responsible for the profound pulmonary changes. Such differences of opinion among pathologists and pharmacologists are important in connection with the clinical management of patients in whom a history of kerosene ingestion is known, or suspected. Up to the present time, early management of kerosene poisoning has been focused on efforts to remove the substance from the body as quickly as possible. However, the lavage of young children who have ingested kerosene may be contraindicated, if aspiration of the kerosene is likely to take place during the emergency lavage procedure. On the other hand, if hematogenous distribution of this toxic agent is an important factor in pathogenesis, early removal of as much as possible of the substance is desirable in order to prevent massive absorption from the gastrointestinal tract. Careful clinical observations in various medical centers have seemed to lend about equal support to the practice of early lavage and to that of refraining from its use. No definite policy has been established apparently by the various clinical groups.

In the May, 1951, issue of *The American Journal of the Medical Sciences,* Richardson and Pratt-Thomas[1] report the results of a study of the "Toxic Effects of Varying Doses of Kerosene Administered by Different Routes." This study was initiated in an effort to determine the degree and extent of pulmonary injury brought about by kerosene administered by various routes. Kerosene was administered to thirty-eight dogs by the following routes: intragastric, intravenous, intratracheal, by stomach tube, and by instillation into a small segment of the small intestine. Sixteen rabbits received kerosene intraperitoneally, by stomach tube, and by the intratracheal route. On the basis of pathologic study, the authors concluded that in most instances it was virtually impossible to distinguish by means of the histologic changes in the lung, which route of administration had been employed, the one exception being that vascular damage in the lung was most marked when the kerosene was administered intravenously. In two of the

animals which had received kerosene by instillation into an intestinal fistula, congestion of the lung was observed, but no definite pneumonia was present. The intimal cells of the blood vessels, however, showed swelling and vacuolization. Intratracheal administration of kerosene resulted in a severe type of pneumonia.

The authors summarize their findings in both the dog and the rabbit in tabular form. An analysis of these findings seems to indicate that in order to prove fatal, a large quantity of kerosene would have to be ingested by the child, if absorption were from the gastrointestinal tract alone. Estimating from these studies in animals, a volume in excess of one pint would have to be swallowed by a child in order to prove fatal, if no aspiration of the substance occurred. On the other hand, very small quantities of kerosene aspirated into the lung resulted in severe pneumonia and fatal outcome. A quantity as small as one teaspoonful aspirated by a young child might be sufficient to cause severe pneumonia and death. In this connection the authors state, "Of primary concern then, is the danger of aspiration rather than consideration of the possible absorption of the oil from the gastrointestinal tract."

On the basis of their observations in laboratory animals, therefore, Richardson and Pratt-Thomas suggest that, where gastric lavage is resorted to, its primary intent should be that of a precautionary measure against regurgitation and subsequent aspiration, rather than a safeguard against gastrointestinal absorption, and that great care be exercised in performing the lavage in order to prevent aspiration during the procedure. It is urged that where the quantity of kerosene ingested is known to be small, no lavage be attempted. The practical suggestion is made that a high cleansing enema might prove just as effective as lavage in removing the kerosene from the intestinal tract, and would not involve the aspiration hazard.

These authors conclude that aspiration is the most usual and the most serious feature of kerosene poisoning as it appears clinically, and that the larger the amount of kerosene aspirated, the more severe the pulmonary damage and the more highly fatal the intoxication.

RUSSELL J. BLATTNER.

REFERENCE

1. Richardson, J. A., and Pratt-Thomas, H. R.: Toxic Effects of Varying Doses of Kerosene Administered by Different Routes, Am. J. M. Sc. 221: 531-536, 1951.

News and Notes

At the annual session of the **Section on Pediatrics of the American Medical Association** held in Atlantic City, June 15, 1951, the following officers were elected for 1951-1952:

Chairman: Dr. Walter B. Stewart, Atlantic City

Vice-Chairman: Dr. Eugene T. McEnery, Chicago

Secretary: Dr. Wyman C. Cole, Detroit

Dr. Woodruff L. Crawford of Rockford, Ill., was elected Section delegate to the House of Delegates, and Dr. Oliver L. Stringfield of Stamford, Conn., alternate.

Dr. Hugh L. Dwyer of Kansas City was re-elected custodian of the Jacobi Fund, and Dr. F. Thomas Mitchell, representative to the Scientific Exhibit.

The annual session of the **Texas Pediatric Society** will be held Oct. 12 and 13, 1951, at Houston, Texas. Guest speakers include Dr. Sidney S. Gellis, Boston, Dr. Lawson Wilkins, Baltimore, Dr, Margaret H. D. Smith, New Orleans, Dr. Gladys Fashena, Dallas, and Dr. Theo Panos, Galveston. The officers of the Society are Dr. T. D. McCrummen, President; Dr. M. C. Carlisle, Secretary; Dr. Edith Bonnet, Treasurer.

Book Reviews

The Postnatal Development of the Human Cerebral Cortex. Vol. IV. The Cortex of the Six-Month Infant. J. LeRoy Conel, Boston, Harvard University Press. Price $12.50.

This volume is the fourth in a series of monographs upon the cytoarchitecture of the normal human cerebral cortex at successive stages of postnatal development. Prior publications related to the newborn (Vol. I), the one-month (Vol. II) and the three-month (Vol. III) infant. All follow the same logical plan of presentation thus facilitating cross-references between them.

The study is published from the Department of Anatomy, Boston University School of Medicine, of which Dr. Conel is Emeritus Professor, and the Department of Pathology, Children's Medical Center, Boston. It is based upon the detailed study of seven well-preserved brains. Contents consist of chapters on lobus frontalis, parietalis, occipitalis, temporalis, insulae, and rhinencephalon; the terminology of von Economo and Koskinas is used. There are abundant illustrations from cresyl violet, Cajal, Golgi-Cox, and Weigert preparations, presented systematically. The drawings from Golgi-Cox material are superb, and illustrate successfully the changing form of the cortical pyramids from field to field. They may be related without difficulty to equally fine photomicrographs of cresyl violet-stained preparations despite a necessary difference between the magnifications used.

The study is in the best traditions of neuroanatomical investigation, and represents the fulfillment of a long felt need of all concerned with the problems of child development for a reliable source book upon the maturation of the cerebral cortex in the human infant.

J. L. O'Leary

Somatic Development of Adolescent Boys. Herbert Rowell Stolz, M.D., and Lois Meek Stolz, Ph.D., New York, 1951, The Macmillan Co., 557 pages. Price $9.00.

This volume reports the authors' findings and conclusions based upon repeated observations of sixty-seven boys over a period of seven years, beginning at ages between 9½ and 12½ years. This study involved various aspects of somatic development and was a part of a broader project conducted by the Institute of Child Welfare, University of California, and at the public schools of Oakland. During the past twenty years, a number of projects have been in operation in this country characterized as "longitudinal" and "multidisciplinary," the former term referring to the periodic reassessment of individuals over all or a part of the growth period, and the latter referring to the interdisciplinary approach to the collection of data and the relating of these data to each other and to the total characterization of the individual. All these projects have differed considerably in the duration and completeness of study of individuals and in the areas in which they have been most successful.

The study by Stolz and Stolz is largely confined to observations of the progress of boys during the exceedingly important and interesting period of adolescence. The report deals only with somatic development, except for one case study which relates it to social and adaptive behavior. These limitations must be taken into account in interpreting the data presented. It is hazardous, for example, to refer to findings as "normal" suggesting that they represent an intrinsic constitutional pattern of progress, without having information to insure that they do not in fact represent temporary reactions to emotional disturbances, dietary restrictions, altered habits of rest and activity, or recurrent illnesses.

The data presented on these boys are primarily anthropometric, including tests of muscle strength, and photographic. These have been obtained on each individual every six months and are presented in tables, distribution and charts of plotted increments. The most unique material consists of the exceptionally good photographs, both of the individuals as a whole, and of the developments in the pubic area.

The conclusions of the authors as to the periods of accelerating, maximum ("apex"), decelerating, and terminal growth and the age and magnitude differences among individuals in these respects are in accordance with previous observations. Detailed studied of the changing increments of growth in the different body measurements of individuals will be of interest at the moment chiefly to students of child development. Of special interest to physicians who care for children during this age period doubtless will be the evidence as to characteristic changes in subcutaneous tissue and weight during early adolescence and in muscle strength a little later. The photographs reveal much as to the characteristic patterns of adolescent development.

H. C. STUART

Werdnig-Hoffmann's Infantile Progressive Muscular Atrophy. Sven Brandt, Copenhagen, 1950, Ejnar Munksgaard. Price Danish kr. 20.

This is a very interesting and thorough monograph on a much debated question. The two questions the author poses for himself are:

1. Is amyotonia congenita a well-characterized disease per se?

2. Are some cases of amyotonia merely congenital forms of Werdnig-Hoffmann's disease?

In nine chapters and 302 pages he elaborates the problem and it seems to this reviewer that he arrives at rather convincing conclusions. The opening chapter is a very good review of the old and new literature on both Oppenheim's disease and on the work published on Werdnig-Hoffmann's progressive muscular atrophy.

Altogether 156 cases are reviewed, all collected from hospitals in Denmark. One hundred twelve of these patients are definitely considered as those suffering from progressive muscular atrophy. Forty-six were established as belonging to the spinal type and two or three probably were of the myogenic type.

Detailed symptomatology is given on the basis of ninety-one cases constituting the author's own material. The value of muscle biopsy is emphasized as an adjuvant in diagnosis. Progression may be slow or very rapid. On the basis of histologic studies the author believes that theoretically we have to differentiate between 2 or perhaps 3 pathologic-anatomic forms: a spinal form, a myogenic form, and possibly a neural form.

Heredity appears to play a dominant role as etiological factor in infantile progressive muscular atrophy. Vitamin E may possibly play a part in the occurrence of the disease. No curative treatment is offered.

The conclusions from this work in the writer's own words are:

It has not been possible through study of the literature or by means of the Danish material of hospitalized children to confirm the existence of any well-characterized disease corresponding to the "amyotonia congenita" described by Oppenheim in 1900. Most of the cases thus designated have been infantile muscular atrophy. On the other hand, muscular flabbiness is a rather common symptom in a number of morbid conditions in childhood—of widely variable character. When the nature of this morbid condition cannot be disclosed, the designation amyotonia congenita may be employed. But it must be realized that this is merely a symptomatic diagnosis that is unsatisfactory and calls for further observation.

ZENTAY.

Editor's Column

A NEW DEPARTMENT

A LITTLE over a year ago, Dr. A. B. Schwartz conceived the idea of listing the articles of pediatric interest appearing in current medical literature. This was taken on as an "Arbeit" by the Department of Pediatrics of the Marquette University School of Medicine under his editorship. The "Current Pediatric References" were mimeographed and have been distributed at approximately monthly intervals. Many hundreds of pediatricians have found it so helpful that they have contributed to its cost, and the mailing list now includes close to 1,000 pediatricians, medical libraries, and all hospitals with pediatric residencies, to whom it has been sent without charge. Reference to the "Current Pediatric References" was made in the November issue of the JOURNAL last year.

A few months ago the suggestion was made that the JOURNAL take over the publication of the Current References. At a recent meeting of the Board it was discussed and approved on three conditions: (1) that Dr. Schwartz and his staff would continue to prepare the material; (2) that it would not curtail the average amount of text now published in each volume; (3) that because of its nature it would not be necessary to include the References in bound volumes.

Dr. Schwartz and the departmental staff at Marquette will continue to edit the Current References. The publishers of the JOURNAL willingly agreed to add ten to twelve extra pages to each issue so that JOURNAL text will not be sacrificed by publishing the References. It has been worked out that the References will follow the editorials in each issue, and precede the advertising pages in the back of the JOURNAL. The References will carry separate page numbers. Thus a JOURNAL reader can separate the References each month for separate filing, or leave as is in the issue. For those who bind the volumes for their library, the References can, if desired, be removed with the advertising pages and discarded, or filed separately.

The JOURNAL takes over with this issue the publication of the "Current Pediatric References," with the expectation that many more of its readers will find it of service and value than those who now receive it.

CYSTIC FIBROSIS OF THE PANCREAS

CYSTIC fibrosis of the pancreas is one of the most discussed diseases in recent years and is an excellent example of the slow way in which knowledge of a condition is gradually gained by the work of many investigators. Starting as a supposedly rare pathological condition of the pancreas recognized at autopsy, it gradually became evident that it was part of a widespread systemic disturbance involving the lungs and intestine among other organs, and that it was by no means such a rare or unusual condition as was first thought. While much of the etiology remains

obscure, as more and more cases have accumulated the evidence points to its belonging to the hereditary genetic group of conditions. Its relationship, if any, to the other members of the celiac group is obscure.

Naturally the clinical recognition of the disease has interested many workers and a number of diagnostic tests have been proposed and studied. These have either been associated with an alteration of intestinal contents brought about by the lack of pancreatic enzymes, or alterations in absorption from the intestine secondary to altered digestion. For a time a complete absence of pancreatic enzymes was the crucial diagnostic criterion, but it was then found that while its absence is significant, in some cases of cystic fibrosis proved at autopsy a certain amount of trypsin was present in the duodenal juices. Thus a diagnosis cannot be excluded by the presence of trypsin. The collection of duodenal juice is not a simple matter, and hence a test for trypsin in the stool was introduced by testing the digestive action of the stool on a gelatin film. The reliability of this test is now questioned as gelatin-liquifying bacteria occur in the stools of children with cystic fibrosis. Absorption curves, particularly vitamin A, have been used, and at one time it was suggested that a deficiency of vitamin A might be an etiological factor, but this is now regarded as a result rather than a cause of the condition and it is not specific. Thus there is still need for more diagnostic methods, and studies of the pathogenesis of the disease.

In this issue we present a new idea for a diagnostic test by Innerfield, Angrist, and Benjamin based on the presence of a low plasma antithrombin level. By its use a diagnosis was made by the authors in an infant 2 weeks of age which was confirmed at autopsy. It has been shown that a high plasma antithrombin level is present in acute pancreatitis where trypsin is high, and the authors conceived the idea that the reverse might be true in cystic fibrosis where it is low. After determining normal plasma levels in young infants they encountered the case reported. However, they found high plasma prothrombin levels in three older infants with the disease, and normal or "low normal" levels in nine children with cystic fibrosis over 3 years of age who had survived the dangerous period of infancy, and had reached the stage where the pulmonary lesions of the disease are more important than the digestive disturbance. From these findings they have postulated an ingenious theory of the pattern of the disease.

A single case and an ingenious theory are far from proving the plasma antithrombin level is of diagnostic value in the disease. It is the feeling of the Editorial Board of the JOURNAL that any suggestions that might ultimately lead to a clarifying of the pattern of the disease, or serve as an aid in diagnosis, should be made available to the many workers interested in the elucidation of cystic fibrosis. Only time and more studies will determine the importance of these observations. Until much more is known about pancreatic cystic fibrosis and its natural history, every bit of new information regarding the condition is of importance, as these bits will ultimately build up the picture as a whole.